DOCUMENT RESUME

ED 336 904 EC 300 636

AUTHOR	Berendes, Heinz W., Ed.; And Others
TITLE	Advances in the Prevention of Low Birthweight. Proceedings from an International Symposium (Cape Cod, Massachusetts, May 8-11, 1988).
INSTITUTION	National Center for Education in Maternal and Child Health, Washington, DC.
SPONS AGENCY	Health Resources and Services Administration (DHHS/PHS), Rockville, MD. Bureau of Maternal and Child Health and Resources Development.; National Inst. of Child Health and Human Development (NIH), Bethesda, Md.
PUB DATE	91
CONTRACT	MCU-117007
NOTE	247p.
AVAILABLE FROM	National Maternal and Child Health Clearinghouse (NMCHC), 38th and R Streets, N.W., Washington, DC 20057 (single copies free).
PUB TYPE	Collected Works - Conference Proceedings (021)
EDRS PRICE	MF01/PC10 Plus Postage.
DESCRIPTORS	*Birth Weight; *Congenital Impairments; Etiology; Infants; Medical Research; Neonates; Nutrition; Perinatal Influences; Pregnancy; *Premature Infants; *Prenatal Influences; *Prevention; *Preventive Medicine; Smoking; Social Support Groups; Stress Variables

ABSTRACT

This proceedings document contains papers addressing trends, determinants, and interventions in preventing low birthweight. Papers have the following titles and authors: "Trends in Rates of Low Birthweight in the United States" (Mary McCormick); "Evolution of the Preterm Birth Rate in France" (Gerard Breart); "The Etiology and Prevention of Low Birthweight: Current Knowledge and Priorities for Future Research" (Michael Kramer); "Support and Stress during Pregnancy: What Do They Tell Us about Low Birthweight?" (Jeanne Brooks-Gunn); "Results of a Three-Year Prospective Controlled Randomized Trial of Preterm Birth Prevention at the University of Pittsburgh" (Eberhard Mueller-Heubach); "Decrease and Rise in Rates of Preterm Deliveries: Haguenau Prenatal Study, 1971-1988" (Emile Papiernik et al.); "The West Los Angeles Prematurity Prevention Project: A Progress Report" (Calvin Hobel et al.); "The South Carolina Multicentered Randomized Controlled Trial To Reduce Low Birthweight" (Henry Heins et al.); "A Prematurity Prevention Project in Northwest North Carolina" (Paul Meis et al.); "The Family Workers Project: Evaluation of a Randomized Controlled Trial of a Pregnancy Social Support Service" (Brenda Spencer); "The Social Support and Pregnancy Outcome Study" (Ann Oakley and Lynda Rajan); "Prevention of Preterm Deliveries by Home Visiting System: Results of a French Randomized Controlled Trial" (Beatrice Blondel et al.); "Smoking Interventions during Pregnancy" (Mary Sexton); "Cervical Cerclage: New Evidence from the Medical Research Council/Royal College of Obstetricians and Gynecologists" (Adrian Grant); "Prevention of Intrauterine Growth Retardation with Antiplatelet Therapy" (Serge Uzan); "Does Calcium Supplementation Reduce Pregnancy-Induced Hypertension and Prematurity?" (Jose Villar); "Magnesium Supplementation in Pregnancy: A Double-Blind Study" (Ludwig Spatling); "An Overview of Trials of Social Support during Pregnancy" (Diana Elbourne and Ann Oakley); "Inhibition of Preterm Labor: Is It Worthwhile?" (Marc Keirse). Appendixes provide the symposium program and list of participants. (DB)

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Advances in the Prevention of Low Birthweight

An International Symposium

Proceedings

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Advances in the Prevention of Low Birthweight

Advances in the Prevention of Low Birthweight

An International Symposium

May 8–11, 1988
Chatham Bars Inn
Cape Cod, Massachusetts

Proceedings

Heinz W. Berendes, M.D., M.H.S., Samuel Kessel, M.D., M.P.H., Sumner Yaffe, M.D., editors

Sponsored by the

Bureau of Maternal and Child Health and Resources Development
Health Resources and Services Administration

and the

National Institute of Child Health and Human Development
National Institutes of Health

of the

United States Public Health Service
Department of Health and Human Services

Produced by

National Center for Education in Maternal and Child Health
Washington, D.C.

Cite as
Berendes, H., Kessel, S., and Yaffe, S. (1991). *Advances in the Prevention of Low Birthweight: An International Symposium*. Washington, D.C.: National Center for Education in Maternal and Child Health.

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Library of Congress Catalog Card No.: 91-60905

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Produced and published by:
National Center for Education in Maternal and Child Health
(NCEMCH)
38th and R Streets, NW
Washington, DC 20057
(202) 625–8400

Single copies of this publication are available at no cost from:
National Maternal and Child Health Clearinghouse
(NMCHC)
38th and R Streets, NW
Washington, DC 20057
(202) 625–8410 or (703) 821–8955 x 254

This publication has been produced by the National Center for Education in Maternal and Child Health under its cooperative agreement (MCU-117007) with the Maternal and Child Health Bureau, Health Resources and Services Administration, Public Health Service, U.S. Department of Health and Human Services.

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THE STEERING COMMITTEE IS INDEBTED TO THE sponsorship of the meeting by the Task Force on the Prevention of Low Birthweight of the Secretary of Health and Human Services and the financial support provided by the Maternal and Child Health Bureau, Health Resources and Services Administration, and the National Institute of Child Health and Human Development, National Institutes of Health of the Public Health Service, United States Department of Health and Human Services. We also acknowledge gratefully the support provided by Ruby Hearn from the Robert Wood Johnson Foundation and Richard Morton from the March of Dimes.

Much of the credit for obtaining manuscripts from the conference participants, editorial corrections and assembling of final manuscript drafts belongs to Martha Gordon who also contributed immensely to the planning and arrangements for the original Chatham conference.

Foreword

A MAJOR DETERMINANT OF INFANT MORTALITY is low birthweight, particularly very low birthweight births. Very low birthweight births (under 1500 grams) account for almost 50 percent of deaths during the first year of life.

Neonatal intensive care is very expensive, particularly for the very low birthweight or severely premature baby, and the cost of neonatal care in the United States has been estimated to be about $2–$2.5 billion per year. In addition, a significant proportion of surviving small premature babies have substantial neurological, behavioral or learning problems as they grow up in society.

Prevention of low birthweight, therefore, has become a major national objective, and research and interventions designed to achieve a reduction in the risk of low birthweight are of the highest priority.

In 1985 Dr. Emile Papiernik organized a meeting entitled "Prevention of Preterm Births" with the subtitle "New Goals and New Practices

in Prenatal Care" which was held in Evian, France, May 19–22, 1985. It brought together scientists from around the world involved in clinical trials or community-based interventions aimed at reducing the risk of preterm delivery. This meeting was highly successful and provided an excellent assessment of the then-ongoing effort to prevent preterm births and served as an important forum for exchange among various investigators. It also emphasized the importance of clinical trials in perinatal medicine.

In this spirit, a steering committee was formed in 1987 to plan for a follow-up conference which was entitled "Advances in the Prevention of Low Birthweight" which many of us affectionately called Evian II. Members of the Steering Committee included Drs. Robert Creasy, Cal Hobel, Woodie Kessel, Irwin Merkatz, Richard Morton, Sumner Yaffe and Heinz Berendes. We wanted to bring together researchers conducting clinical trials or community-based interventions aimed at reducing the risk of low birthweight. It was our belief that expanding knowledge through this state-of-the-art review of strategies for preventing low birthweight—the principal determinant of risk for poor survival and or life-long morbidity—will greatly enhance our ability to provide quality health services to vulnerable populations and significantly contribute to the advancement of maternal and child health in the United States and worldwide.

The papers presented in this volume cover a broad array of scientific investigations which includes biological exposures, clinical trials of the effect of social support during pregnancy on birth outcome, the use of antiplatelet therapy to prevent preeclampsia, and possible beneficial effects on the risk of preterm delivery through calcium supplementation or magnesium supplementation. A concluding discussion attempted to identify directions for future research.

There was a spirited exchange about scientific intervention projects in urban populations and international collaboration. Should we test single or multiple interventions, especially in inner-city populations? Dr. Papiernik's intervention strategy in France consisted of multiple interventions. His program also appeared to be most effective in low- or medium-risk women rather than high-risk women. Overwhelming social problems in inner-city populations in the United States may create immense obstacles to the evaluation of the Papiernik educational intervention model and therefore socially high-risk groups may be inappropriate for testing of these interventions. In designing social support trials what is meant by social support? Patients' perception may be different from investigators' intention. There is urgent need for an improved risk assessment tool although the current imprecision of risk assessment may be an accurate reflection of our very limited understanding of the determinants of preterm delivery or intrauterine growth retardation.

Considerable attention was devoted to a discussion of methodological issues and endpoints of interventions such as biological variables and or proxies for mortality and morbidity.

We have the sincere hope that this series of conferences which Dr. Emile Papiernik initiated in Evian in 1985 has made a significant contribution to our knowledge and ability to improve the health and well-being of future generations.

SECTION

I

Trends

Trends in Rates of Low Birthweight in the United States

Marie McCormick, M.D., Sc.D.

Introduction

Presenting this topic to this audience represents a classic example of the "coals to Newcastle" phenomenon. This phenomenon will become particularly evident as the discussion unfolds, since it relies so heavily on the work of several here. What I hope to achieve, therefore, is to summarize what can be characterized as "what we already know" by way of introduction to this conference.

Importance of Low Birthweight

What do we "know" about the importance of low birthweight (LBW)? In the United States, infant mortality rates remain relatively high compared to other industrialized countries.[1] Most infant deaths now occur in the neonatal period, and the majority of neonatal deaths occur

among LBW infants.[4] The persistence of high levels of infant mortality is not because we have failed to achieve dramatic declines in infant mortality over the past 20 years. These declines, however, reflect our success in reducing the mortality rates among small babies; indeed, our birthweight-specific mortality rates may be among the best in the world. A recent report from the U.S. Congress' Office of Technology Assessment (OTA)[5] illustrates this point. Over the past 20 years, the mortality rate among very tiny infants has declined dramatically, while the proportion surviving with severe to moderate handicap remains small. Thus, the proportion of survivors in reasonable health has increased.

In spite of this increase, the persistent minority who survive with appreciable levels of handicap is of concern. Moreover, the cost of care for such tiny infants is substantial,[5] and remains high even when compared to our seemingly exorbitant costs for a "normal" delivery.[6] Thus, both on a health and on a financial basis, low birthweight presents an important problem.

Meaning of Low Birthweight

Likewise, we know that a discussion of low birthweight is really a shorthand notation for the adequacy of a complex physiologic process: intrauterine fetal growth. At each week of gestation, there is a distribution of birthweights. Using a cut-off point or grouping based on birthweight, then, clearly captures a group that is heterogeneous for duration of gestation.[7] Both birthweight and gestational age are related to mortality,[7] and for many purposes gestational age is the better indicator of risk. Birthweight tends to be more accurately measured and less likely to be missing from our vital statistics data, however, and has therefore become the measure most frequently used in data from the United States.

Let us also quickly acknowledge that referring to birthweight groupings or cut-offs reflects a somewhat arbitrary point along a continuum of risk and mortality. In other words, 2500 g or 1500 g does not represent a biologic discontinuity, but a cut-off point which has achieved utility as a marker of risk through repeated usage. Because certain groupings or cut-off points have achieved currency and their meaning is well understood, we will continue to use them in this discussion.

Let us return, however, to pursue the point of intrauterine growth a bit further. Low weight at birth may result from one of two processes, either independently or in combination: (1) shortened duration of gestation, or (2) less growth than would be anticipated for a given length of gestation. Among the former, growth (height and weight) is appropriate for gestational age (AGA), but delivery has occurred before 37 weeks of completed gestation. Unlike growth retardation, the causes of preterm labor and the factors which increase the risk of it require further elucidation.[8] Among the latter, which is attributed to intrauterine growth retardation (IUGR), the infants are judged to be small for gestational age (SGA) by being born less than the established percentile for growth for a given gestational age. A variety of conditions are associated with IUGR.[9] An SGA infant may also be premature. At a given gestational age, an SGA infant is less likely to survive than an AGA infant where higher weight confers an advantage. At a

given birthweight, however, maturity confers the advantage to the SGA infant until term.[8]

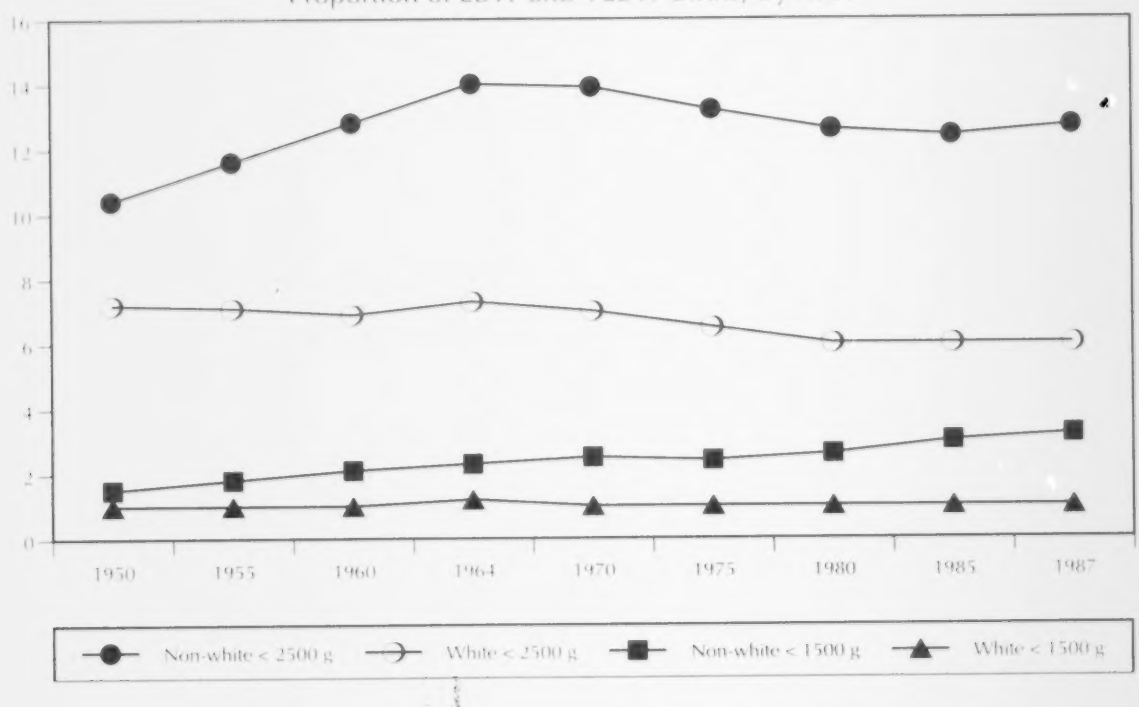
Changes over Time

What, then, has the recent U.S. experience been in terms of trends in low birthweight over time? Unfortunately, the rates of low birthweight are not changing very much. The proportion of live births less than 2501 g has decreased slowly by a little more than 15 percent in the past 15 years (see figure 1.1). The proportion of live births less than 1501 g, however, has remained the same or risen slightly. Thus, while the proportion of LBW births has declined overall, this population is now weighted toward the lower end of the birthweight distribution with a higher proportion of the very high-risk births.[9] Most births less than 1501 g, both AGA or SGA, are also preterm. These trends suggest that much of the decrease which we have experienced is in low birthweight due to IUGR. This interpretation is supported by other analyses.[9,10] What factors may be invoked to explain this trend or lack of trend?

Factors Associated with Trends in Low Birthweight

The most striking factor in the U.S. experience remains the racial disparity in rates of low birthweight.[11] The LBW rate for black Americans is twice that of whites and other racial/ethnic groups, and is well above the

Figure 1.1
Proportion of LBW and VLBW Births, By Race



Marie McCormick

objective set for 1990. This higher rate of LBW is paralleled by higher infant mortality rates, although unlike LBW, the mortality rates are declining.[1] What accounts for this difference?

One hypothesis is that there are genetic or inherited differences in birthweight distributions. Support for this argument can be derived from studies which document an intergenerational correlation of birthweight.[2,3] In addition, analyses which compare the full range of birthweights between ethnic groups reveal that the entire birthweight distribution for blacks is shifted downward.[4] Such shifts suggest that standard cut-off points, such as 2500 g, do not connote the same degree of risk for black births as for nonblack births. Indeed, for a given low birthweight, black infants have lower birthweight-specific mortality rates than whites. Adjusting for birthweight distributions results in higher mortality rates throughout the birthweight distribution for blacks, however, supporting the argument that they are at a disadvantage.[4] While the potential genetic contribution of race to birthweight and the appropriate statistical techniques for adjusting for differences in birthweight distribution require further study, disparities in birthweight among subgroups within the black population using conventional markers of birthweight risk suggest room for improvement within the current genetic endowment. It is these disparities among subgroups which we will explore further.

Epidemiologic tradition has identified three sociodemographic characteristics which are associated with increased risk of low birthweight: (1) young maternal age, (2) low maternal educational attainment, and (3) marital status.[5] Blacks remain at a disadvantage by having higher proportions of births to women characterized by these factors than whites. For both groups, however, the proportion of mothers less than 18 years of age and mothers with less than 12 years of education (graduation/school-leaving norm for the United States) has decreased; the proportion of mothers who are unmarried has increased, but this probably does not connote the same degree of risk now as it did in more permissive times. If anything, then, the relative risk for these variables has declined, which represents a trend that is not consistent with the trend in low birthweight.

These factors are not independent. A woman who initiates childbearing early is less likely to complete school and to be married. Kleinman and Kessel have examined this question for selected states in the years 1973 and 1983.[6] When these factors are analyzed in combination, the relative differences between blacks and whites diminish among the high-risk women. In other words, women who are at high risk by virtue of their age and/or educational attainment have similar pregnancy experiences regardless of race. Thus, part, but not all, of the racial disparity can then be attributed to the fact that black births are more likely to occur among women who fall into the high-risk categories.

If this is the case, then, what is it about maternal age or education which leads to the higher rates of low birthweight? Although blacks are twice as likely to be adolescent mothers, and substantially more likely to be very young mothers, the relative risk of a low birthweight birth for young black mothers compared to older black mothers is less than the relative risk for young white mothers compared to older white mothers. These findings are consistent with the

increased risk of even "low-risk" black mothers noted earlier. They are also consistent with an interpretation that age per se does not confer risk. Such an interpretation is reinforced by the findings of special programs for adolescent mothers which reduce the risk of adverse outcome, but only to the level of older mothers in their environment. A similar picture emerges with education.[13] Thus, changes in sociodemographic characteristics of mothers account for a relatively small percent of the trends in low birthweight.

If education or age per se does not account for what we see, then perhaps the questions should be rephrased. Is there some factor which is associated with early child bearing, low educational attainment, and perhaps black race which leads to adverse outcome? In other words, are these factors markers for other, truly causal factors, factors which would pertain to both whites and blacks, but to blacks disproportionately? An immediate candidate leaps to mind: poverty.

Consideration of poverty as a causal factor suggests a number of pathways by which the risk of low birthweight might be increased. Since much of the remainder of the conference will be spent in discussion of many of these factors and potential interventions to ameliorate their effects, I will restrict the following discussion to illustrative examples.

One aspect of poverty is a restriction of financial resources to obtain needed goods and services. A necessary, if not totally sufficient, service or set of services in attaining positive pregnancy outcomes is adequate prenatal care. Inadequate prenatal care is higher among low-income groups and among the high-risk groups previously noted.[14] This deficit for mothers in the United States reflects, in part, gaps in payment for maternity services which stem from our medical care financing customs: 17 percent of all women of childbearing age lack insurance for maternity services. Even with private insurance coverage for most medical services, maternity care may only be partially covered or not covered at all, since pregnancy is considered an elective event not amenable to classical insurance actuarial techniques. Another 10 percent of women of childbearing age rely on public resources, but even those eligible for public support may find obtaining prenatal care difficult. Participation may be limited by complex application processes and inadequate fee schedules to cover the usual costs of maternity services.[5]

Consistent with a relationship between prenatal care and pregnancy outcome is the fact that groups identified as high risk are more likely to receive inadequate care.[5] Moreover, the proportion of women potentially at higher risk for adverse outcome who start their care in the first trimester has changed little over the past few years, which is again consistent with the lack of change in pregnancy outcome. As with maternal sociodemographic characteristics, however, elimination of those with less than adequate care would have only a modest effect on the rate of low birthweight (a 12–15% reduction). Even combining this with reductions of those with sociodemographic risk results in a decrease of only 29 percent in the LBW rate for whites and 30 percent in the rate for blacks.[15] Thus, access to prenatal care is only part of the problem.

Constrained financial resources may also indicate an inability to obtain other necessities for a good pregnancy outcome. One which has received attention is adequate nutrition. Controversy exists as to the proportion of the

U.S. population experiencing hunger or an inability to obtain the needed daily caloric intake to sustain weight. Total caloric deprivation, however, is less likely than inappropriate mixture of basic foods and other nutrients. Since it is not clear what an "appropriate mix" should be, the exact deficits in the diets of the poor cannot be readily identified. That there are deficits is suggested by the data on the effectiveness of the WIC program (Special Supplemental Food Program for Women, Infants and Children).[17] This is not unalloyed evidence, however, since this program provides a mixture of services, as well as food supplements. The area of appropriate nutrition represents an area of further research.

Consideration of other aspects of the effects of poverty reveals additional mechanisms by which it may contribute to adverse pregnancy outcome. Substantial evidence exists to support a relationship between poverty and poor health generally. With regard to pregnancy outcome, maternal health factors would include the (1) relationship of specific health problems as complications of pregnancy, and (2) health practices which might affect both maternal and child health. Among the latter are the use of cigarettes, illicit drugs, and excessive alcohol. In addition, certain types of physical activity may increase the risk of poor pregnancy outcome, as suggested by the data for women with physically and emotionally stressful jobs which require long commutes.[18] In the United States as a whole, approximately 30 percent of women smoke and 55 percent drink before their pregnancies, but a proportion become abstinent during pregnancy, so that close to half of U.S. women do neither during their pregnancies.[19] National data on smoking do not reveal much disparity between the rates of black and white women, and black women tend to drink less. The role of illicit drugs is notoriously difficult to assess both due to the reluctance of individuals to report drug use and the uncertain content of "street" drugs. A well-established correlate of poverty is the lack of employment. Thus, such health-related habits would appear, at first blush, not necessarily to be related to racial inequities in birthweight.

It would seem, however, that the questions ought to be more sophisticated than that. First, the lack of paid employment does not rule out stressful labor, given the lack of financial resources to invest in labor-saving household appliances. More importantly, such factors may confer a different level of risk for women whose health may already be compromised by long-term exposure to health risks associated with disadvantaged environments. In a recent study of the mothers of young infants in central Harlem, 10 percent had been hospitalized in the year since delivery; 12 percent rated their health as fair or poor; and 14 percent scored in the distressed range on a mental health scale. Moreover, some of the risk factors for poor pregnancy outcome also correlated with poor maternal health subsequent to pregnancy, suggesting an interactive effect.[20]

More current information is needed on the health problems and behaviors of women of childbearing age as they might affect their capacity for reproduction. Perhaps our very low maternal mortality rates have provided a sense of security which may require further re-examination, although black/white disparities in this health status indicator may have caused some

concern.[21] We do collect health data on women of childbearing age through the National Health Interview Survey (our Harlem data parallel national data on black women), the National Natality Survey, and birth certificate analyses. It is difficult to establish, however, how the subset of women who bear children may differ from the larger group of women of childbearing age, since at any one time only a minority of women are experiencing pregnancy and childbirth.

Seeking prenatal care and changing health habits to improve pregnancy outcome require a certain amount of anticipation or planning. The groups most at risk, however, are the ones least likely to have intended to be pregnant.[7] These findings suggest that, in addition to prenatal care, low-income women may have difficulty in achieving access to family planning services as well. It is small wonder that such access may be difficult to sustain given the fact that reproductive care for low-income women may be spread across several types of clinics: family planning clinics, gynecology clinics, clinics for sexually transmitted diseases, abortion clinics, and obstetric clinics (many with legally dictated separations of facility and staff).[22]

Moreover, overcoming barriers to care and modifying unhealthful behaviors requires motivation, energy, and support.[23] As the earlier data on maternal mental health suggest, other aspects of disadvantaged environments also adversely affect women in this sphere. Again in this same cohort of young mothers, environmental stress as measured by stressful life events is high, but social support—as measured by the ability to identify an individual by name and relationship to provide help in six common situations—is not. These factors relate to maternal health, and some studies have implicated such combinations in the risk of adverse pregnancy outcome.[24]

Summary and Suggestions

In summary, the low birthweight rate in the United States remains high, with only slow decreases and a predominance of premature births. These high rates reflect the persistence of socioeconomic disadvantage, especially among blacks. The factors underlying these trends are complex, and this complexity suggests that change will not come easily.

In view of this complexity and lack of ready explanation for the persistence of low birthweight, our own experiences and those of others suggest some questions and approaches which, while not exhaustive nor even perhaps original, may be useful in the next two days. The first question relates to our understanding of "risk." The majority of low-income women, or black women, or poorly educated women, or very young women have normal birthweight (NBW) infants. We tend to treat women with these characteristics as if they were homogeneous, and yet each of these labels masks considerable heterogeneity. Perhaps we should be considering more "micro" studies on the risk factors within communities and trends in outcomes at a more local level with more focused data to understand the nature of this heterogeneity.

Secondly, even with established risk factors, we need to be more specific about the mechanisms by which such factors alter risk and the potential modifiers of both the effect of the risk factor and interventions to ameliorate its effect. We are recurrently taken aback by the

relatively small contribution of prenatal care to changes in birthweight, yet the relevance of the individual components of that package of services which we call prenatal care to the current problems affecting pregnancy outcome require further examination. Furthermore, examples of successful programs are rarely described in sufficient detail to assess the generalizability of the intervention. Likewise, the modifiers which may contribute to the persistence of a well-recognized risk like cigarette smoking are not well described. For example, in our study, environmental stress and lack of social support did not contribute directly to birthweight differences, but were clearly associated with smoking behavior in pregnancy. Additionally, we need better information on how sociodemographic and behavioral risk factors translate into biological processes affecting fetal growth.

Finally, we may need to pursue some more complex intervention models.[9] A comparable problem is the mental retardation seen in children who come from disadvantaged backgrounds. There are now several well-documented randomized trials of successful interventions, and their success provides support for expanding national programs for early childhood education. These experiences, however, rely on well-developed and explored conceptualizations of early childhood development and specific curriculums aimed at the identified deficiencies of sufficient intensity to achieve the desired results. It is hoped that the presentations over the next few days will raise us all to this more sophisticated level of approach to this complex problem.

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Evolution of the Preterm Birth Rate in France

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INTRODUCTION

During the 1970s in France, reduction in the preterm birth rate was considered a major objective in perinatal medicine.[1-3] This objective was included in a perinatal program implemented between 1970 and 1975.[4] This program included incentives to increase prenatal care, outpatient clinics for high-risk women, and educational programs. It was followed in 1975 by a series of measures, including regulations for the working conditions of pregnant women and implementation of a home visiting system. Since 1981, no new specific programs or actions have been developed.

The aim of this paper is to trace the evolution of the preterm birth rate in France. The paper will be divided into two parts. The first part corresponds to the evolution of the

preterm birth rate between 1972 and 1981, based on national data, and the second corresponds to the evolution between 1984 and 1986, based on hospital data.

Evolution of the Preterm Birth Rate Between 1972 and 1981

Material and methods

The data here presented are derived from three national surveys conducted in France in 1972, 1976, and 1981 on representative samples of birth.[7] Each sample was obtained by a two-stage (maternity unit, and deliveries within the unit) sampling procedure (see table 2.1). For every delivery included in the survey, a questionnaire was completed. The representativeness of the data was assessed by comparison with data on all births. The main objective of these surveys was to evaluate, at the national level, the results of the perinatal program.

Results

Table 2.2 shows that, between 1972 and 1981, the preterm birth rate decreased from 8.2 percent to 5.6 percent. It should be noted that this decrease was observed for births occurring before 34 weeks' gestation, as well as for births occurring between 34 and 36 weeks' gestation.

This reduction in the preterm birth rate was accompanied by a reduction in the rate of low birthweight births between 1984 and 1986 (see table 2.3). This reduction was observed for very low birthweights as well.

During this same period, prenatal care changed dramatically in France (see table 2.4), both quantitatively and qualitatively. For example, the percentage of women with 7 or more prenatal visits increased from 22 percent to 55 percent. The temporal relationship between the modification of prenatal care and the decrease in preterm births is not sufficient to prove a causal relationship. Other factors may have had an impact on the rate of preterm birth. Among them, the demographic factors are the most important. Table 2.5 shows that women who delivered in 1981 were at lower risk for preterm birth than women who delivered in 1972. There were fewer women younger than 20 years of age, fewer women with 3 or more previous pregnancies, and fewer women with a short interval since the previous birth.

To take into account the evolution of these factors, standardized rates of preterm birth were computed (see table 2.6). The 1972 population was used as the reference population. The comparison between crude and standardized rates shows that changes in demographic factors explained only one-third of the decrease in the number of preterm births.

Comments

In addition to the changes in demographic factors, there have been other changes. Not all of the changes led to a decreased risk in preterm birth, however; some of the changes, in fact, had the opposite result. Therefore, changes in maternal characteristics, as evaluated through the data collected, do not appear sufficient to explain the decrease in preterm birth. It is likely that the modification in prenatal care (including nonmedical care) had an

impact on the overall rate of preterm birth.

Since many interventions have been implemented at the same time, ranging from increased use of betamimetics to regulations concerning working conditions, it is very difficult to evaluate the efficacy of any one particular intervention.

It is now accepted[1] that some of the proposed interventions have been overused or misused. However, in agreement with what is known about risk factors of preterm birth,[2] which are multiple and cannot explain all of the cases of preterm birth, it is believed that a reduction in the preterm birth rate could not be obtained through a single intervention. Instead, a comprehensive program is needed which includes several types of interventions, among which obstetricians, midwives, and social workers could choose one (or several) specifically adapted to each woman according to her living and working conditions as well as to the symptoms she presents. Since the known risk factors explain only part of the overall rate of preterm birth,[2] a program to decrease preterm birth should not be limited to high-risk women, but should be targeted to all women in the general population.

Evolution of the Preterm Birth Rate Since 1983

In recent years, it seems that the views of French obstetricians[3] concerning prevention of preterm birth have changed. This change seems linked to two main causes: First, concerns about the safety of very commonly used drugs, such as betamimetics; and, second, progress in neonatalogy. Another factor which may have influenced French obstetricians is the trend, for fetal growth-retarded fetuses, toward an increase in premature termination of pregnancy to prevent long-term handicap. Those factors have raised some questions concerning the recent trend in the preterm birth rate in France. In order to collect the necessary information, a survey was conducted among several maternity units. The results are presented here.

Material and methods

To obtain information on the recent evolution of the preterm birth rate, as well as its determinants, a questionnaire was sent to 30 maternity units known to be users of the same type of computerized record. These units belong to an association called *Association des Utilisateurs d'un Dossier Informatise en Perinatologie, Obstetrique et Gynecologie*. The purpose of the questionnaire was to collect data for the three more recent years (1984, 1985, and 1986) on the preterm birth rate; birthweight and mortality rates; social, demographic, and medical characteristics of the population; and policy adopted for the prevention of preterm birth. Among the 30 units approached, only 9 were able to provide complete data. They are located in different parts of France (see figure 2.1), and 20,000 women per year deliver in these units.

Results

In the maternity units studied (see table 2.7), the preterm birth has increased from 6.6 percent to 7.7 percent. According to impor-

tance of prematurity (< or > 34 weeks), or to induction of labor (artificial or spontaneous), an increase was observed for spontaneous preterm delivery no matter what the gestational age, whereas an increase in induced preterm delivery was observed only for very low gestational age (< 34 weeks). Table 2.7 shows that more than one-quarter of the increase in preterm births was directly related to an increase in preterm induction for termination of pregnancy.

To screen the possible factors which might have led to an increase in spontaneous preterm birth, the evolution of some risk indicators (e.g., frequency of women with previous preterm birth, maternal age under 20 years, unemployment, use of betamimetics, and first prenatal visit at the unit during the first trimester) was examined during this period. Among the five indicators studied, two—the percentage of women receiving betamimetics and the percentage of women coming to unit during the first trimester—varied markedly (see table 2.8). Both frequencies decreased during the period.

Comments

Even if the increase in preterm births observed in some hospitals in France cannot be considered as representative of the actual trend at the national level, the data collected showed that an increase in the preterm birth rate has been observed at the same time as modifications in preventive attitudes have been observed. Modifications in obstetricians' attitudes have been observed (as demonstrated in the increase in preterm induction and restrictions in the use of betamimetics), as well as modifications in women's attitudes as reflected by the percentage of women starting their prenatal care, after the first trimester, at the outpatient clinics of the units. This change may not be due only to changes in women's attitudes, however, but also to changes in general practitioners' attitudes, who could have delayed the referral to the maternity unit, or to socioeconomical problems, which could have made it more difficult to access the maternity units under study.

The modification of the obstetricians' attitudes seems to be recent,[7] as does the upward trend in the preterm birth rate. Several of the maternity units which have experienced a recent increase in the preterm birth rate had documented a decrease during the 1970s.

The increase in preterm birth has not been observed only in French hospitals. Table 2.9 shows that it has been observed in Sweden, Norway, and Iceland as well.[8]

Conclusion

From the data presented here, it can probably be concluded that a portion of the preterm births can be prevented. This statement is based on the decrease observed in France during the 1970s and the recent increase in some hospitals. This variation in trend in "spontaneous" preterm birth suggests the possible effect of some environmental factors. These factors could be social, demographic, or medical, since the observed change in the preterm birth rate corresponds to changes in preventive policies (e.g., increase in medical intervention

during the first period, and decrease during subsequent periods) as well as changes in social factors. The type of data presented here does not allow any conclusions to be drawn concerning the factors which are responsible for the decrease or the increase in preterm birth. Such conclusions can only be drawn from experimental surveys. The results of the randomized controlled trials presented at this symposium, as well as those presented at the Evian meeting,[9] do not lead to clear conclusions concerning which interventions can reduce preterm birth and which interventions cannot. These conflicting and disappointing results might be due to the fact that prevention of preterm births can only be obtained through multiple interventions, each of them alone resulting in too few benefits to be observed in an experimental study.

Another conclusion which can be drawn from the hospital data is that prevention of preterm birth cannot be considered as an objective per se, but as a means to reduce long-term handicaps. In some circumstances, obstetricians will induce preterm termination of pregnancy because of fetal distress, and an increase in preterm birth rates might lead to better long-term results. Therefore, the overall preterm birth rate can no longer be considered a good indicator of perinatal results. A distinction must be made between spontaneous and induced preterm deliveries, and perinatal programs should be evaluated based on long-term outcome or on indicators which are highly correlated with long-term outcome. Such indicators remain to be defined.

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Statistical Findings: Evolution of Preterm Birth in France

Table 2.1
Design of the National Surveys

	1972	1976	1981
Sampling fraction	0.0137	0.0068	0.0068
Number of units	637	420	390
Number of deliveries	11,254	4,685	5,508

Table 2.2
Evolution of Gestational Age (National Data)

	1972 Percentage	1976 Percentage	1981 Percentage
Number of Weeks			
< 34	2.4	1.7	1.2
34–36	5.8	5.1	4.4
37–39	37.0 $p < 0.01$	34.9 $p < 0.01$	37.9
40–42	50.8	54.0	53.1
43+	4.0	4.3	3.4
≤ 36	8.2 $p < 0.01$	6.8 $p < 0.05$	5.6

Table 2.3
Evolution of Birthweight (National Data)

	1972 Percentage	1976 Percentage	1981 Percentage
1500 g	0.8	0.7	0.4
1500–1999 g	1.2	0.9	1.0
2000–2499 g	4.2	4.9	3.8
2500–2999 g	19.1 NS	17.9 $p < 0.01$	18.0
3000–3499 g	41.8	42.3	41.3
3500–3999 g	25.5	26.4	27.5
4000 g +	7.4	6.9	8.0
< 2500 g	6.2 NS	6.5 $p < 0.01$	5.2

Table 2.4
Evolution of Prenatal Care (National Data)

	1972 Percentage	1976 Percentage	1981 Percentage
Number of prenatal visits			
< 4	15.3	10.6	3.9
4	35.4	29.1	16.5
5–6	27.1 $p < 0.01$	26.4 $p < 0.01$	24.7
7 +	22.2	33.9	54.9
Hospitalization during pregnancy	7.3 $p < 0.01$	13.0 $p < 0.01$	15.6
Betamimetics	*	8.9 $p < 0.01$	14.7
Care by general practitioner only	*	20.8 $p < 0.01$	8.8

* *not available*

Table 2.5
Changes in Demographic Factors (National Data)

	1972 Percentage	1976 Percentage	1981 Percentage
Maternal age			
< 20 years	9.9	8.5	6.0 $p < 0.001$
≥ 40 years	2.4	1.1	0.9
Number of previous pregnancies			
3 +	18.3	14.1	15.4 $p < 0.001$
Previous birth			
≤ 17 months	21.6	15.4	10.2 $p < 0.001$

Figure 2.1
Maternity Units Involved in the Study

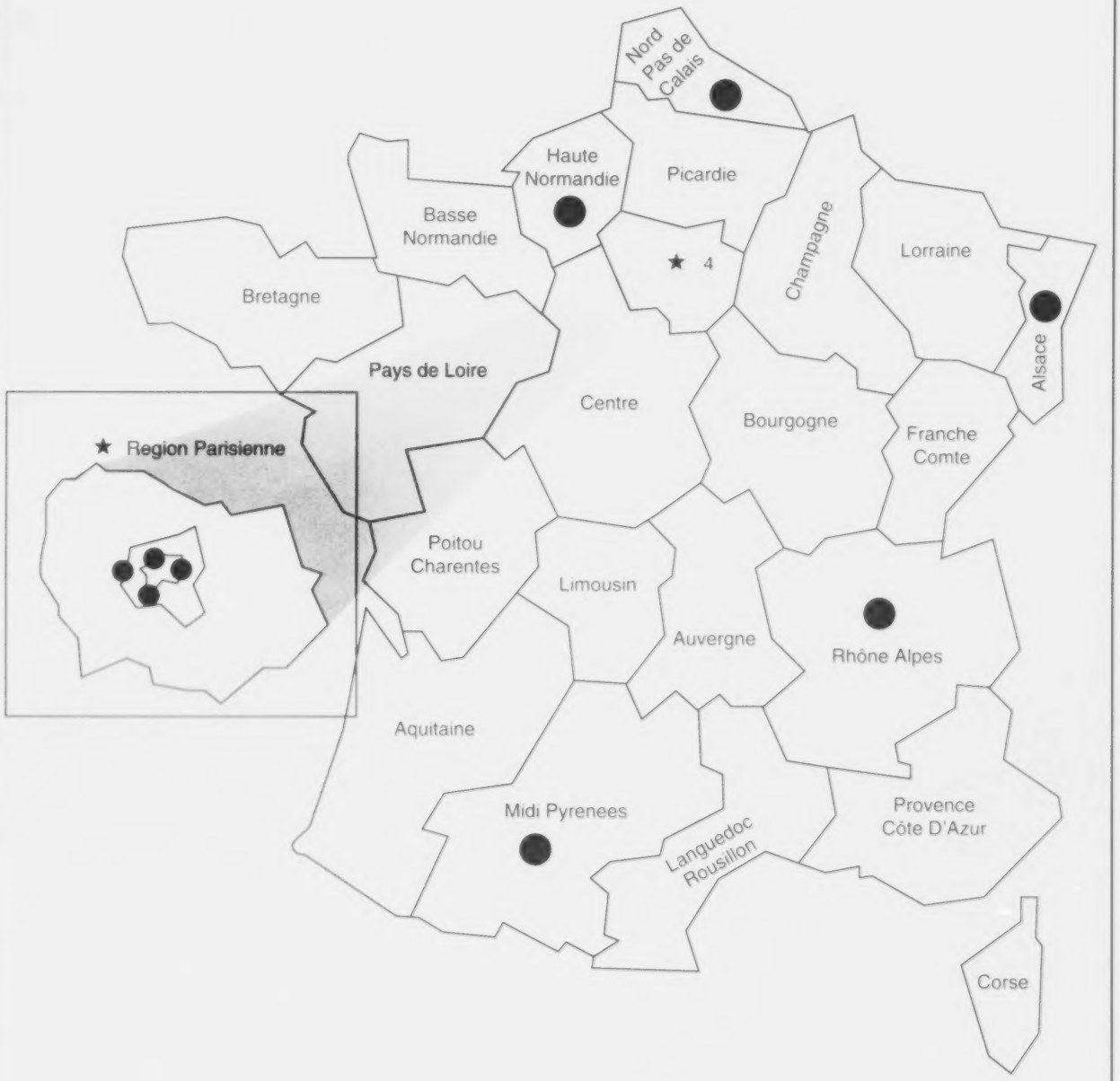


Table 2.6
Evolution of preterm birth rate
(Crude and Standardized* Rate, National Data)

	1972 Percentage	1976 Percentage	1981 Percentage
Crude rate	8.2	6.8	5.6
Standardized rate	8.2 NS	7.8 $p < 0.05$	6.7

* *Standardization on age, number of previous pregnancies, and interval between births.*

Table 2.7
Evolution of Preterm Birth (Hospital Data)

	Year* 1	2	3
≤ 34 weeks	2.6	2.9	3.3
spontaneous	1.5	1.6	1.8
induced	1.1	1.3	1.5
35–36 weeks	4.0	4.4	4.4
spontaneous	2.3	2.5	2.7
induced	1.7	1.9	1.7

* Years 1, 2 and 3 generally represent 1984, 1985, and 1986.

Table 2.8
Evolution of Risk Indicators (Hospital Data)

	Year* 1 Percentage	2 Percentage	3 Percentage
Betamimetics Use	21.8	20.5	17.5
1st visit during 1st trimester	50.5	45.3	44.3

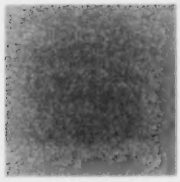
Table 2.9
Preterm Birth Rate (≤ 36 Weeks) in Nordic Countries

	1979	1980	1981	1982	1983
Denmark	4.9	5.0	4.9	4.8	4.8
Finland	—	—	—	—	5.2
Iceland	2.6	2.7	3.0	3.1	3.4
Norway	4.9	4.9	5.1	5.0	5.2
Sweden	4.5	5.6	5.8	5.9	6.1

Source: Papiernik, E., Breart, G., and Spira, N. (1986). *Prevention de la naissance prématurée.* INSERM, 138.

SECTION

II



Determina

The Etiology and Prevention of Low Birthweight: Current Knowledge and Priorities for Future Research

MICHAEL S. KRAMER, M.D.

INTRODUCTION

In both developing and developed countries, low birthweight (LBW), that is, birthweight less than 2500 g, is a major risk factor for neonatal mortality and for subsequent morbidity and impaired functional performance.[1] The design of interventions to prevent LBW depends on a sufficient understanding of its etiologic determinants. Although it is widely acknowledged that causality of LBW is multifactorial, there have been considerable confusion and controversy about which factors have independent causal effects, as well as the quantitative importance of those effects. One of the major reasons for this confusion and controversy has been a failure to distinguish LBW caused by a

short duration of gestation (i.e., premature delivery) from LBW caused by intrauterine growth retardation (IUGR).

Prematurity is defined as a gestational age less than 37 weeks. IUGR, which is also referred to as small for gestational age (SGA) or small for dates (SFD), is usually defined as birthweight less than the 10th percentile for gestational age for a "standard" reference population. (It is obvious from these definitions that babies can be premature or growth retarded without necessarily weighing less than 2500 g. Thus, while it is true that LBW babies are either premature or growth retarded or both, the converse is not necessarily the case, particularly in well-nourished populations from developed countries.)

The distinction between prematurity and IUGR is of crucial importance because they differ considerably not only in etiology, but also in terms of their prognostic significance and relative incidence in different settings.

For example, premature infants are at greater risk for developing hyaline membrane disease, apnea, intracranial hemorrhage, sepsis, retrolental fibroplasia, and other conditions relating to physiologic immaturity. Several of these conditions are responsible for the far greater neonatal mortality in premature babies.

On the other hand, IUGR infants are more likely to have deficits in growth, and at least some of these deficits appear to be permanent. As to relative incidence, Villar and Belizan have analyzed data from 25 developing and 11 developed regions.[2] In developing countries, most LBW births appear to be due to IUGR, whereas in developed countries (especially those with the lowest LBW rate), most are due to prematurity. Thus, the focus of preventive efforts, both in terms of clinical and public health policy and future research priorities, will differ in different settings depending on the relative incidence of prematurity and IUGR.

Reported discrepancies concerning the etiology of LBW may have explanations other than the IUGR-prematurity distinction. Primary among these is the matter of association versus causation; that is, "markers" of LBW versus true causal determinants.

The issue here is not merely the theoretical concern for "scientific purity." Rather, the association-causation distinction is of considerable practical import for improving public health, since an intervention will succeed in reducing LBW only if it affects a true causal factor. Many of the potential determinants are highly associated with one another, and adequate control for confounding is thus required to identify and quantify their causal effects. Two possible statistical explanations for the reported discrepancies concern the portion of the birthweight or gestational age distribution (e.g., middle v. lower tail) on which a determinant acts and inadequate statistical power in studies with small sample sizes.

In an attempt to help clarify these issues and synthesize the recent literature, I recently undertook a methodologic review and meta-analysis of the English and French literature published between 1970 and 1984.[3] Although several issues have been further clarified over the last several years, I believe the results of that review still provide a reasonable synthesis of our current state of knowledge about the etiologic determinants of prematurity and IUGR. The following section summarizes the methods and results of that review.

Current Knowledge

Summary of 1970–84 Review

The 1970–84 review was restricted to singleton pregnancies occurring in women living at sea level without chronic illness. Factors of extremely low prevalence (e.g., maternal rubella infection or uterine malformation) were not considered, because even though such factors will be of great importance to the individual women in whom they occur, they are not responsible for a significant portion of IUGR and prematurity on a population-wide basis. Also excluded from consideration were medical complications of pregnancy, such as pregnancy-induced hypertension, abruptio placentae, placenta praevia, and premature rupture of the membranes. In my view, such conditions should be considered as intermediate outcomes of pregnancy. Their inclusion in a multifactorial model of causation will inevitably lead to an underestimate of the effect of factors whose impact on intrauterine growth or gestational duration may operate through one of the conditions.

After these restrictions and exclusions, 43 factors (or groups of factors) were left for assessment. These are listed in table 3.1. The literature search began by examining the subject catalogue of the World Health Organization library for books and monographs published since 1970. A similar search was carried out for review articles listed in *Index Medicus* over the same time period. These were supplemented by a MEDLINE computer search for the years 1982–84. Finally, a "snowball" procedure was used, by which each article or book chapter located was examined for further references published since 1970, followed by the references cited in those secondary reports, and so on. Each reference identified by the search was examined for data concerning 1 or more of the 43 factors.

Methodologic standards were established *a priori* for studies of each candidate factor. These included such general aspects of research design as definition of the target population and study sample, description of study participation and follow-up rates, clear demonstration of the appropriate temporal sequence between the factor and outcome, and the use of an experimental research design (where feasible and ethical). The remaining standards pertained to the potentially confounding variables requiring control for nonexperimental studies and differed according to the factor under assessment.

Studies satisfactorily meeting (SM) or partially meeting (PM) the standards were selected for further analysis. SM studies fulfilled the majority of the predetermined criteria. PM studies gave some attention to rigorous design and analysis, but fulfilled less than half the criteria. For several of the factors, certain standards were judged to be of overriding importance in assigning an SM or PM rating. Based on the studies selected for further analysis, each factor was assessed for the existence of an independent causal effect on birthweight, gestational age, prematurity, and IUGR. If an independent causal effect was judged to be demonstrated on the basis of the combined evidence of the selected studies, and sampling variation could be excluded as an explanation (i.e., $p < .05$), the effect size was extracted from each study. For birthweight or gestational age, this may have taken the form of the difference in means from a randomized trial or a matched cohort study, an adjusted difference derived from an analysis

of covariance, or a regression coefficient from a multiple linear regression analysis. For prematurity and IUGR, the corresponding effect size extracted was the relative risk or odds ratio adjusted for potential confounders by using matching, the Mantel-Haenszel procedure, or multiple logistic regression analysis.

The extracted effect sizes were then weighted by the study-specific sample sizes to yield an overall estimate for each factor. Finally, using available data on the prevalence of each demonstrated causal factor in different population groups, etiologic fractions were calculated for prematurity and IUGR. The etiologic fraction (EF), which is also known as the population attributable risk or attributable risk percent, is defined as the proportion of IUGR or prematurity in a population that is attributable to a given factor. It is calculated as follows:

$$EF = \frac{P(RR-1)}{P(RR-1) + 1}$$

where P is the prevalence of the factor in the population and RR is its corresponding relative risk or odds ratio.

The literature search using the combined snowball procedure identified a total of 921 publications. Of these, 895 or 97.2 percent, were successfully located and reviewed. Although a majority of the reports originated from developed countries in North America and western Europe, a large number also came from developing countries in Latin America, India, Africa, and southeast Asia. The total number of factor assessments carried out was 1,566. Even though some of the reports did not contain original data bearing on any of the factors, this total far exceeds 895, since many reports provided data on several factors.

Factors with well-established direct or indirect (i.e., acting via one or more direct-acting factors) effects on intrauterine growth are listed in table 3.2. Those with effects on gestational duration are contained in table 3.3. In order to illustrate the quantitative importance of the well-established direct determinants, I have constructed pie diagrams in which the size of the pie slices is roughly proportional to the etiologic fraction for each of the indicated factors. Figure 3.1 is the pie diagram for IUGR in a typical rural developing country in which malaria is moderately endemic but pregnant women do not smoke. Nonwhite racial origin is probably responsible for a large proportion of IUGR in developing countries with high prevalences of black or Indian racial origins. The other major factors are poor gestational nutrition, low prepregnancy weight, short maternal stature, and malaria. It is important to emphasize that, of the five leading factors, three may be modifiable in the short term: Gestational nutrition, prepregnancy weight, and malaria.

Figure 3.2 shows the pie diagram for a developed country in which 40 percent of the women smoke during pregnancy. In this setting, the most important single factor by far is cigarette smoking. This is followed by poor gestational nutrition and low prepregnancy weight. The three leading factors are all potentially modifiable, once again, with obvious implications for public health intervention. Although the overall size of the pie is smaller than in the developing country setting (i.e., the IUGR rate is lower), a larger proportion of existing fetal growth retardation may be preventable.

A pie diagram for the well-established direct determinants of prematurity in the developed country setting is shown in figure 3.3. Of the five factors with well-established direct causal effects, cigarette smoking and low prepregnancy weight are modifiable but account for a relatively small proportion of premature births. The major message from figure 3.3 is that the majority of prematurity occurring in the population remains unexplained. In part, this large gap in our knowledge reflects the far less intense previous effort in studying gestational duration as compared to intrauterine growth. This has been especially true in developing countries.

Recent Developments

Since this assessment was carried out, a number of studies that bear on prevention of prematurity have been published in developed country settings. Although I have undertaken no formal assessment of the literature appearing since 1984, I would like to highlight three areas in which research has shown promise for preventing prematurity: (1) Reduction of maternal work and physical activity during pregnancy; (2) identification and close surveillance of women at high risk for premature delivery; and (3) treatment of genital tract infection/colonization.

The available evidence permits no definitive conclusions as to whether work and physical activity during pregnancy are beneficial, harmful, or irrelevant for gestational duration. Recent evidence does suggest that prolonged strenuous or stressful work activities, aerobic endurance-type exercise continued into the third trimester, and upright posture may increase the risk of prematurity, and that moderate sport and exercise may reduce it (at least among well-nourished women in developed countries),[9-11] but further studies are required. A Subcommittee on Dietary Intake and Nutrient Supplements During Pregnancy has been convened by the Food and Nutrition Board, National Academy of Sciences, to synthesize the information available in this area. This committee should be publishing its report within the next several months. [Editor's note: This publication was released in 1990. It is entitled *Nutrition During Pregnancy*, and is available from the National Academy of Sciences.]

Another area of intense recent research activity concerns identification and close surveillance of women at high risk for premature delivery. The assessment of high risk is based on multifetal gestation, uterine malformation, incompetent cervix, or a history of previous premature birth or second trimester abortion. Surveillance has used such modalities as frequent pelvic examinations, teaching mothers to recognize early signs of uterine contractions, and, most recently, ambulatory tocodynamometry (i.e., home monitoring of uterine contractions using a portable recording device). The evidence from intervention studies involving these modalities is inconclusive,[13-18] but some of the results have been quite impressive and certainly are sufficient to justify further research. It should be emphasized, however, that even if effective methods can be developed for preventing prematurity in women at high risk, the overall impact on a population-wide basis will depend on the predictive value of the risk assessment and on the proportion of all premature births that occur in women classified as at high risk.[19]

Finally, sufficient evidence exists concerning the possible etiologic role of bacterial vaginosis and genital tract infection or colonization with such organisms as *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Gardnerella vaginalis*, species of *Bacteroides*, and other anaerobes to justify randomized antibiotic trials in women colonized with these organisms in the second and early third trimesters.[3,20-24]

Several such trials are already in progress in the United States, including a large multicenter study supported by NICHD, and the results are eagerly awaited. Recent evidence also indicates that genital tract infection colonization in women with preterm labor is associated with failure of conventional tocolytic therapy.[25,26] Further trials should be undertaken of broad-spectrum antibiotic treatment as an adjunct to routine tocolysis in women with preterm labor or rupture of the membranes.

General Methodologic Issues

Since a major focus of this symposium is intervention studies—and, particularly, randomized clinical trials—aimed at reducing the rate of prematurity and IUGR, I will conclude this paper with a summary of several key methodologic issues that apply generally to such trials. These issues are: Individual versus group randomization, blinding and unblinding, the effect of participation on outcome, selective subject participation, and compliance.

Individual versus Group Randomization

Random allocation of treatment to each subject maximizes the likelihood that treatment assignment remains unpredictable by either the subject or the investigator. It also tends to result in groups which are similar for both known and unknown susceptibility factors that could otherwise confound the treatment effect. Thus, randomization of individual subjects is a prime desideratum for a methodologically sound clinical trial. For some types of interventions, however, random assignment by individuals can actually be detrimental because interaction between subjects may lead to consequent "contamination" of the intervention, and, hence, a biased comparison.

For example, randomizing half of the women within a given work setting to a change in posture or position during work (e.g., by allowing them to sit rather than stand while performing certain tasks) or to a shortening of the work day is likely to lead to a "spill-over" effect to the other half of the women working in the same setting who are randomized to the control intervention. The result would be a diminution of the difference in the treatments received by the two groups of women and the possibility of a false negative result. In such situations, where relatively closed, naturally formed groups are capable of modifying the intervention allocated to individuals within those groups, group randomization appears preferable to the randomization of individual subjects.

Unfortunately, group allocation carries some hazards not inherent in the individual approach. Since individuals within a group cannot necessarily be regarded as independent from one another, the effective sample size is reduced by the extent of within-group dependence. Ideally, the solution to this problem is

to base the statistical analysis on the number of work settings (e.g., companies or factories) rather than on the number of individual women. Because of the large number of work settings required in such studies, however, this strategy will often be infeasible.

A more practicable approach would involve the use of a pre-intervention study to demonstrate that individuals in two or more different work settings experience similar birthweight and gestational age distributions before institution of the intervention. Equivalent pretrial results increase the plausibility that any differences in outcome that occur when those work settings are exposed to different interventions during the actual trial are attributable to the intervention, rather to potentially confounding differences between the different settings. The randomized interventions could even be introduced in selected settings sequentially over time so that efficacy could be evaluated via before and after comparisons, as well as concurrent comparisons between intervention and control work settings.

Blinding and Unblinding

Blinding of study subjects and observers (i.e., double blinding) is highly desirable in placebo-controlled interventions involving drugs. Such a design is clearly feasible for such interventions as placebo controlled antibiotic trials. It is obviously infeasible, however, for reduction in physical activity or ambulatory monitoring of uterine contractions. For the latter types of interventions, observers involved in assessing gestational age and birthweight can usually be kept blind, but the women themselves cannot.

Mothers' knowledge of the group to which they have been assigned can then lead to a biased treatment comparison. This is especially true when the comparison is one of intervention versus no intervention. Mothers who receive the intervention will obviously be aware that they are among the "chosen," and this awareness may create a feeling of specialness that can exert a profound (and uncontrolled) placebo effect.

Although subjects in these types of intervention studies cannot be kept blind to the actual intervention they receive, they can and should (when ethically defensible) be kept blind to the interventions being compared and to the study hypothesis. Placebo-type control interventions can be designed in ways to facilitate this type of blinding. For example, women enrolled in a trial to assess the effect of reduction in maternal energy expenditure could be asked to participate in a study of work changes. Changes in work activities would be implemented in both intervention and control groups, with the former changes focusing on energy-reducing maneuvers and the latter involving other changes not expected to reduce maternal energy expenditure. In this example, blinding would be relatively easy to maintain, as long as the two study groups worked in distinct geographical settings.

Effect of Participation on Outcome

Study participation can change behavior, even in the control group, and the behavioral change itself may affect the outcome under study (this is known as the Hawthorne effect). It seems likely that the feeling of specialness attendant upon participation in an intervention

study might itself have a beneficial effect on certain outcomes. Study participation might, for example, serve as a form of social support and thus mitigate the effect of stress, thereby reducing the risk of premature delivery. Because the potential magnitude of the benefit of the intervention may be limited (the ceiling effect), the end result may be either a smaller treatment difference or no significant difference, and thus a false negative result concerning the effectiveness of the intervention.

If possible, investigators should attempt to keep study subjects unaware that they are being studied, or at least unaware of the main outcomes being compared. For most types of interventions, however, keeping study mothers in the dark will not be ethically defensible. In those cases, the potential for a Hawthorne effect should be acknowledged by the study's investigators, and inferences should be mitigated accordingly.

Selective Subject Participation

In general, participation rates tend to be lower in intervention studies than in observational studies. Although statistical power can be maintained by approaching additional women, those who agree to participate may be quite different from those who do not. Unfortunately, therefore, the study's findings may not be generalizable to all mothers who are eligible to receive the intervention in the real world.

Investigators should make every effort to keep track of, and include in all resulting publications, both the numbers and relevant characteristics of all women who accept and decline participation. The characteristics of importance are those that, independent of the intervention under study, can affect the susceptibility to develop IUGR or prematurity. Socioeconomic status, age, parity, height, prepregnancy weight, cigarette smoking, and alcohol consumption are examples of the types of characteristics that should be considered.

Compliance

Many of the interventions currently under investigation for prevention of low birthweight involve some effort by study women to comply with the assigned intervention. To the extent that women do not comply, differences in outcome between the intervention and control groups will be correspondingly reduced. Once again, this can lead to false negative inferences about the intervention's efficacy. Investigators should routinely include strategies for stimulating and maintaining subject compliance, as well as measuring its extent. Monitoring of compliance could involve pill counts or tracer labels detectable in urine for interventions involving medication, or onsite observations for such interventions as reduction in maternal work physical activity or recording of uterine contractions.

The main statistical analysis for any of these intervention studies should be based on the intention to treat, that is, a comparison of all women (or groups or other units of randomization) randomized to the two study groups, not just those who comply. A secondary analysis comparing those subjects with good compliance, however, can suggest what the potential *biological* efficacy of the intervention is and point to efforts required in future trials to achieve the compliance necessary to demonstrate overall treatment effectiveness.

Priorities for Future Research

Future intervention studies should focus on modifiable factors of potential quantitative importance for which the evidence of causal impact on prematurity or IUGR is inconclusive. In developing countries, the emphasis should be on preventing IUGR. Based on current knowledge, one promising intervention concerns reduction of strenuous maternal work during pregnancy, particularly in women with poor prepregnancy or gestational nutrition. Improved prenatal care (in terms of timing, frequency, or content) should be another high-priority target. Because a few studies have shown a beneficial effect of folic acid supplementation, further randomized trials in women with folate-deficient diets should also be undertaken. Although the available evidence concerning iron deficiency and anemia indicates no significant effect on intrauterine growth, additional trials of iron supplementation in anemic or iron-deficient women may be necessary to rule out such an effect. Other intervention trials might involve supplementation with other vitamins or trace elements (e.g., calcium or zinc) and reduction in exposure to indoor smoke.

In developed countries, future research should focus on preventing prematurity. The most promising avenues to pursue at this time include reduction in strenuous or stressful maternal work and physical activity, monitoring of uterine contractions in women at high risk for premature delivery, and treatment of women with bacterial vaginosis or colonization by certain genital tract pathogens.

In both developing and developed countries, these research priorities present formidable methodologic and practical challenges. A randomized trial design should be used whenever feasible and ethical. As I have discussed, however, the vagaries of human behavior, especially during a period as psychologically sensitive as pregnancy, can affect trial participation, compliance, blinding, and outcome. Thus, a study's use of this design does not necessarily confer certainty on its conclusions. The planning, execution, and analysis of intervention studies to prevent low birthweight provide great scope for creative science and high hope for improved public health.

Acknowledgment

From the Departments of Pediatrics and of Epidemiology and Biostatistics, McGill University Faculty of Medicine. This work was carried out while Dr. Kramer was a National Health and Research Scholar of the National Health Research and Development Program, Health and Welfare Canada.

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Statistical Findings: The Etiology and Prevention of Low Birthweight

Table 3.1

Factors Assessed for Independent Causal Impact on Intrauterine Growth and Gestational Duration

A. Genetic and Constitutional Factors

Infant Sex* Racial/Ethnic Origin* Maternal Height* Maternal Prepregnancy Weights Maternal Hemodynamics
Paternal Height and Weight* Additional Genetic Factors

B. Demographic and Psychosocial Factors

Maternal Age† Socioeconomic Status† Marital Status Maternal Psychologic Factors

C. Obstetric Factors

Parity* Birth or Pregnancy Interval Sexual Activity Intrauterine Growth and Gestational Duration in Prior Pregnancies
In Utero Exposure to Diethylstilbestrol§ Prior Induced Abortion Prior Stillbirth or Neonatal Death
Prior Infertility Prior Spontaneous Abortion§

D. Nutritional Factors

Gestational Weight Gain* Vitamin B$_6$ Caloric Intake* Energy Expenditure, Work, and Physical Activity
Protein Intake/Status Iron and Anemia Folic Acid and Vitamin B$_{12}$ Calcium, Phosphorus, and Vitamin D
Other Vitamins and Trace Elements Zinc and Copper

E. Maternal Morbidity During Pregnancy

General Morbidity and Episodic Illness* Malaria* Urinary Tract Infection Genital Tract Infection

* *Established direct determinants of intrauterine growth include infant sex, racial/ethnic origin, prepregnancy weight, paternal height and weight, maternal height and weight, parity, prior LBW, gestational weight gain, caloric intake, general morbidity, malaria, cigarette smoking, alcohol consumption, and tobacco chewing.*

† *Established indirect determinants of intrauterine growth include maternal age and socioeconomic status.*

§ *Factors with well-established direct causal impact on gestational duration include prepregnancy weight, prior prematurity, prior spontaneous abortion, in utero diethylstilbestrol exposure, and cigarette smoking.*

‖ *Factors with well-established indirect causal impact on gestational duration include maternal age and socioeconomic status.*

Figure 3.1

Relative Importance of Established Factors with Direct Causal Impacts on IUGR In a Rural Developing Country with Endemic Malaria

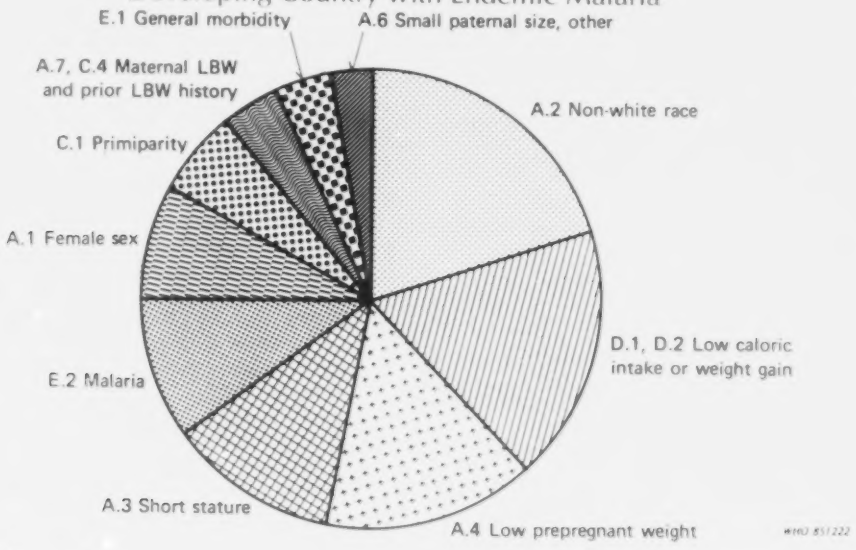

E.1 General morbidity
A.6 Small paternal size, other
A.7, C.4 Maternal LBW and prior LBW history
A.2 Non-white race
C.1 Primiparity
A.1 Female sex
D.1, D.2 Low caloric intake or weight gain
E.2 Malaria
A.3 Short stature
A.4 Low prepregnant weight

Figure 3.2

Relative Importance of Established Factors with Direct Causal Impacts on IUGR In a Developed Country Where 40 Percent of Women Smoke During Pregnancy

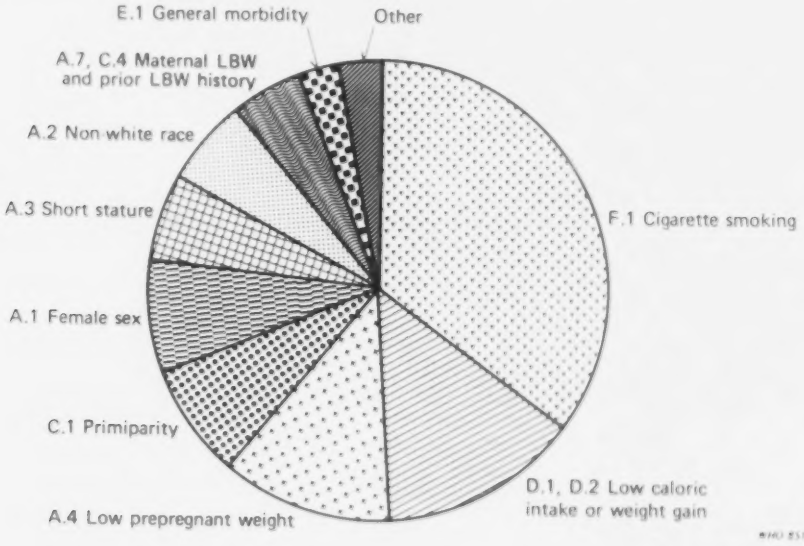
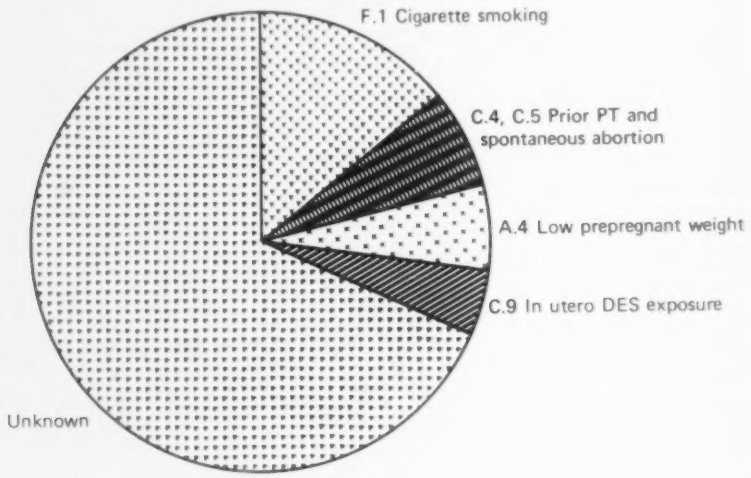


Figure 3.3

Relative Importance of Established Factors with Direct Causal Impacts on Prematurity in a Developed Country Where 40 Percent of Women Smoke During Pregnancy


F.1 Cigarette smoking
C.4, C.5 Prior PT and spontaneous abortion
A.4 Low prepregnant weight
C.9 In utero DES exposure
Unknown

Stress and Support During Pregnancy: What Do They Tell Us About Low Birthweight?

JEANNE BROOKS-GUNN, PH.D.

INTRODUCTION

The remarkably high incidence of low birthweight births in the United States over the past 25 years remains very much a puzzle. While timely antenatal care is associated with better birthweight outcomes, the increases in the proportion of women receiving early care in the last two decades have not resulted in comparable declines in the low birthweight rate. In addition, race differentials in the proportion of low birthweight have not changed during this historical period (there is a 2:1 ratio between blacks and other racial and ethnic groups).[1,2,3]

It is estimated that perhaps 40 percent of the variance in low birthweight births is due to environmental and psychosocial factors (The Institute of Medicine 1985 report identified health behavior, psychosocial and physical stress, demographic conditions, and toxic expo-

sure as principle nonmedical risk factors).[4] To solve the puzzle, then, we need to know which environmental and psychosocial events are contributing to low birthweight; how physiological, environmental, and psychosocial conditions each contribute to pregnancy outcome in a relative sense; and what the links might be between environmental events or psychological states and subsequent physiological changes leading to early labor.

The focus in this chapter is on which psychosocial events are important, rather than how they actually might initiate early labor or what they contribute over and above medical factors. Direct proximate links between psychosocial factors and actual physiological consequences have not been studied in great detail.[5] Most of the studies conducted to date center on health behaviors whose affects are believed to be cumulative in naure (e.g., smoking, postponing antenatal care, and eating poorly); psychosocial states that are thought to influence the pregnant woman over a relatively long period of time (e.g., anxiety, depression, and stress experienced due to negative life events); and environmental events that are chronic (e.g., poverty, low level of education, and crowded living conditions). Since the human fetus is believed to be relatively protected (at least primates seem to be less influenced by negative environmental conditions than are rodents),[6-8] continuous exposure to a negative condition is thought to be necessary for a poor pregnancy outcome. Indeed, the possible effects of short-term stressors in addition to chronic stressors or multiple negative life events on the long-term mental and physical health of the postpartum human are just beginning to be studied.[9,10]

Five issues are addressed in this chapter: (a) the commonly held beliefs about psychosocial contributions to poor pregnancy outcome, particularly as they relate to anxiety, stressful life events, and social support; (b) the association of these psychosocial factors with health behavior; (c) the importance of considering the context in which these health behaviors and psychological factors occur, especially with regard to ethnicity and social class; (d) the usefulness of different models for studying the effects of health behaviors and psychosocial factors simultaneously; and (e) the implications of both beliefs and conceptual models for the types of preventative programs that have been and might be initiated.

Stress and Social Support: Effects on Pregnancy Outcome

The following assumptions permeate the popular and clinical literature about pregnancy:

- Anxiety and emotional distress during pregnancy result in poor pregnancy outcomes.
- The occurrence of negative life events, and the stress associated with coping with such events, negatively influence a pregnancy.
- Social support acts as a moderator, or as a buffer, from the untoward effects of stressful life experiences and emotional dysfunction.
- Emotional dysfunction and stress have direct effects on pregnancy outcomes (via some as yet not-well-specified physiological pathways) over and above health behaviors, such as smoking, nutrition, and exercise.

- Persistent race differences in neonatal outcome are accounted for in part by the fact that blacks are more likely to live in poverty, have lives that are more stressful, have experiences that are more difficult and anxiety-producing, and have fewer available social supports (both formal and informal).

Results linking obstetric and neonatal outcome to emotional states, negative life events, and social support will be reviewed separately.[3]

It is important to realize, however, that all three factors are associated with current notions about stress. The physiological effects of emotional distress or upset have been documented.[11,12] Often, emotional upset is presumed to be caused by negative life events and ameliorated by social support.

Stress is often considered to occur when an individual is confronted with an event (a) that is perceived as threatening; (b) that requires a novel response; (c) that is seen as important (i.e., demands a response); and (d) for which the individual does not have an appropriate coping response available.[13,14] Stress has been associated with physical illness as well as negative emotional states. Stress is believed to influence illness via changes in neuroendocrine functioning, immune system responses, and health behaviors. Thus, stress might influence pregnancy outcome directly (in terms of physiology) or indirectly (in terms of health behavior).

It has been hypothesized that social support ameliorates these effects at different points between the appraisal of an event as stressful and a physical illness. As illustrated by Cohen and Willis,[15] social support may alter the individual's initial determination that an event is indeed stressful, thereby helping the individual cope successfully, so that the event is not perceived as stressful (see figure 4.1). In addition, social support may alter the individual's behavioral or physiological response to an event actually perceived as stressful. Support may help individuals regulate health behaviors, lessen their responses to stress, or help solve the problem.[15,16]

Anxiety and Emotional Distress

The idea that emotional upset is associated with poor pregnancy outcome has a time-honored history. Folk wisdom has linked stress in pregnancy to abnormalities in neonates as described in the Old Testament, by Greek physicians, and in the writings from the Middle Ages to the present.[7,17] Currently, associations between emotional states and obstetric and pregnancy outcome have been examined, with a number of these studies being reviewed recently by Istvan[7] and earlier by McDonald.[18] Typically, this literature has focused on anxiety, and, to a lesser extent, on depression, anger, and hostility. In the 1950s and 1960s, nonstandardized measures of anxiety were often used, making it difficult to make across-study comparisons. In addition, most studies have focused on the more trait-like (i.e., presumably more stable and enduring) aspects of anxiety and emotional upset, rather than on the more situation-mediated aspects of anxiety (i.e., presumably less continuous or enduring). This is surprising, given that the folk wisdom usually mentions emotional distress caused by a specific situation and that theories such as that of Seyle consider short-term stressors as well as

long-term adaptation to difficult situations. Finally, some (but not all) studies are prospective in nature. In retrospective studies, it is quite likely that women with preterm infants will reinterpret past events or emotional states as having been more stressful.[19] No studies have followed a sample of women prior to conception through pregnancy and delivery. Thus, no baseline data exist with which to compare levels of anxiety during pregnancy, or prepregnancy differences between women who report high and low levels of anxiety during their pregnancies. Even studies of changes in anxiety throughout the pregnancy are rare.

With these caveats in mind, what do the studies (focusing primarily on the prospective ones), tell us about the belief that emotional upset affects poor obstetric outcome? The two studies conducted in the 1950s[20,21] did not support the thesis and indeed, if anything, provided evidence of the opposite (that is, anxiety was associated with better obstetric outcome). Of the nine studies reviewed by Istvan[7] from the 1960s, seven reported some evidence of link between anxiety and poor obstetric outcome and two did not.[22-30] By the 1970s, when more standardized scales were being used with greater frequency, of six studies (excluding those with very small samples), two provided confirmatory[31,32] and four had discomfirmatory findings.[33-36] Two studies from the 1980s found no significant direct links.[37,38] Of particular interest is the study of Beck and colleagues,[37] who assessed state rather than just trait anxiety and found no associations with obstetric outcome during the third trimester. A measure taken just before delivery, however, was associated with length of labor. Thus, of 19 studies, 9 report evidence for the commonly held belief, and 10 do not.

Turning to neonatal, rather than obstetric outcomes, the folk wisdom is comparable. Indeed, the assumptions about links are substantiated in the nonprimate literature. In most (but not all) studies of rodents, emotional stress (as inferred by environmental conditions such as crowding, and exposure to light, heat and noise) is associated with poor neonatal outcome (i.e., prematurity and low birthweight). The human literature is less convincing. Only looking at prospective studies, three have reported positive associations[39-41] and eight have not.[22,27,29,34,37,38,42] All of these studies used birthweight or Apgar scores as their neonatal outcomes.

In brief, the commonly held beliefs about maternal emotional upset, at least when assessed as anxiety, are not validated by the current literature. While more support exists for links with obstetric than neonatal outcomes, the most recent studies using standardized measures of emotional distress have not always supported the conclusions reached in the obstetric outcome literature of the 1960s.

Stressful Life Events

The occurrence of many life events is believed to constitute a stressor with implications for emotional and physical well-being. Indeed, events such as the illness or death of a spouse, child, sibling, or parent, as well as the occurrence of many events simultaneously or in a short period of time, have been associated with many illnesses, either as an etiological or an exacerbating factor.[43-45] Recent work has documented changes in immunological and corti-

sol functioning in the aftermath of negative events.[44-46] In addition, the occurrence of multiple life events as well as chronic stress often associated with some life events and conditions has been shown to place individuals at increased risk for decrements in well-being.[47-49] A huge body of literature exists exploring the conditions under which multiple life events are likely to be detrimental and to buffer the individual from untoward effects.[50,51,46,51]

Research attempting to demonstrate links between negative life events and obstetric outcome is not as extensive as that on emotional distress, possibly because most of the theoretical work on life events is fairly recent. Of the six studies reviewed that looked at obstetric outcome, results are mixed. Looking at "situational" stresses (perhaps the precursors to negative life events), Grimm and Venet found no associations with obstetric outcomes.[47] In the 1970s, several studies found positive associations, but only when considered in relation to social support.[51,52,52] The findings from these three studies are difficult to interpret, however, and caution should be taken in considering them as confirmatory.[7] In addition, two recent studies either reported no association or a "marginal" one.[38,53]

In four prospective studies focusing on neonatal outcome, an association between negative life events and neonatal status (i.e., low birthweight or premature contractions and or deliveries) was found in two;[19,53] a mediated effect was found in the third, where life events were associated with a "sense of permanence," which in turn was negatively associated with neonatal problems;[55] and no effect was found in the fourth.[41] In three retrospective studies, two reported associations between negative life events and prematurity.[50,58] In brief, the literature is inconclusive with respect to associations between negative life events and poor outcomes.[7]

Social Support

The availability and use of social support buffers the individual from the possible deleterious effects of negative life events.[59-61] Indeed, some research validates this claim, even though questions have been raised as to whether what is being measured is a direct effect of life events upon social support or an interaction of events and support.[59] In addition, social support may affect psychological state (and, by inference, physiological state) directly, rather than through interaction with life events.

It is commonly believed that social support protects the pregnant woman or neonate from the untoward effects of stressful life events or emotional distress. Perhaps the most often quoted study is that of Nuckolls, Cassel, and Kaplan,[62] in which the occurrence of negative life events and the availability of social support were assessed. While neither was associated with obstetric outcome, of the women who had a number of life changes, those with low social support were more likely to have obstetric problems than those who had high social support. This study has been widely cited as evidence for the importance of social support for buffering the pregnant woman against the possible negative effects of stressful life events. As Istvan[7] points out, however, the result was based on a difference of five cases between the two groups, and few studies have appeared in the literature that have replicated the original

finding. In one, which was a retrospective study, an interaction between life change and complications was found; specifically, high life changes and low social support were associated with neonatal problems (low life changes and low social support were inexplicably associated with labor and delivery problems, however).[58] In another, duration of support was associated with neonatal complications, both directly and indirectly.[55]

Health Behavior and Stress

In the discussion to date, and in almost all of the studies just reviewed, no consideration has been given to possible associations between psychosocial factors and women's health-related behavior. The implicit premise is that they affect pregnancy outcomes directly, via physiological processes related to stress. An alternative possibility is that they play an indirect role, operating through health behavior. That is, emotional distress, social support, and negative life events might influence women's compliance with health regimes, or at least may co-occur with particular health behaviors. For example, in the study by Newton and Hunt, 54 life events were associated with low birthweight, but this correlation was not significant after controlling for cigarette smoking. In another study demonstrating a link between life stress and prematurity, the mothers of preterm infants were more likely to smoke and drink than the mothers of term infants (unfortunately, the effects of substance use in mediating the original association were not examined).[62]

In a study of 500 disadvantaged minority women in Harlem who were first seen during their first or second clinic visit, a somewhat different tack was taken. No differences in the proportion of low birthweight births were seen for schooling, work, maternal age, or psychosocial factors such as stressful events, social support, and emotional functioning, while smoking and adequacy of care were associated with low birthweight. Indirect effects were found, however, as smoking status was associated with the women's adequacy of prenatal care, stressful events, social support, mental health, and prior adverse pregnancy outcome.[63,64] Current smokers were less likely to have adequate care in the current pregnancy and more likely to have experienced a prior adverse neonatal outcome than nonsmokers. They had experienced fewer negative life events than nonsmokers; however, they were less likely to be living with a husband or boyfriend (see Table 4.1).

In brief, previously documented associations between psychosocial factors and birthweight may be mediated by health behaviors. That is, social support and emotional functioning may influence health behaviors such as smoking and prenatal care, which in turn influence pregnancy outcome. In addition, a different mix of psychosocial factors may be relevant for different health behaviors; for example, in the above-mentioned study, the psychosocial correlates of timing of antenatal-care onset were somewhat different than those for smoking.

Contributions of Ethnicity and Poverty

Thus far, ethnicity and poverty have not been considered, even though both are known

to be associated with low birthweight births and both form the context in which a number of psychosocial conditions occur. For example, the occurrence of negative life events is associated with emotional and physical well-being.[65-67] In addition, undesirable life events are more prevalent in the economically disadvantaged, the poorly educated, the female, the young, and the unmarried.[68-70] Not only are certain groups likely to experience negative events, but these very same groups are more vulnerable to them; that is, they will be more likely to exhibit psychological disturbance when confronted with negative events, as Kessler has suggested.[71,72]

Such vulnerability may be due, at least in part, to the unavailability of resources, as demonstrated elegantly in several studies, where the joint occurrence of many stressful events and low social support are more predictive of psychological distress than either one is separately.[64,73-75] One study has demonstrated this interaction in pregnant women: high support and personal control reduced the impact of negative life events significantly.[73] Another approach to considering the importance of race and poverty as possible mediators, or as codeterminants of psychosocial functioning, considers high-risk populations. Demographic characteristics, such as race, age, and education, and risk factors on a population-wide basis, may lose some of their discriminatory power within low-income groups. That is, increased risk may be confounded with disadvantage. For example, in the Harlem study, no associations were found between birthweight and the traditional demographic risk factors such as maternal status, education, occupational status, and ethnicity (Hispanic and black). Thus, the risk associated with these factors may be more generally due to poverty status. In addition, few or relatively weak associations between birthweight and psychosocial factors were found. This may be because poverty confers increased risk for both environmental stress and poor pregnancy outcomes.[65]

A final approach involves the possibility of interactions between sociodemographic factors and health behaviors. In one study, black mothers with preterm deliveries had more medical and social conditions than those without preterm deliveries, but the strongest medical predictor, hemocrit values, was associated with social risk factors (e.g., being unmarried, a teenager, on welfare, or having a low level of education). The authors suggest that combinations of medical and sociodemographic factors are most likely to be predictive of preterm delivery and that models including such combinations are more likely to reduce the black-white differences than models of sociodemographic conditions alone.[76,77]

Models to Study Psychosocial Factors and Health Behaviors

It is important to consider the conceptual models that are implicit in the studies conducted to date. Indeed, one of the shortcomings of the literature is that simple, direct-effects models are usually tested, even though the phenomenon under study is better represented by mediated or indirect-effects models. We also need to consider whether relations are best characterized as linear, cumulative, or threshold.

At least five models are relevant (see Figure 4.2).

1. The first is considered a simple, direct-effects model, where the links between social support, emotional distress, and life events on the one hand and poor pregnancy outcome on the other are examined. Most of the studies conducted to date have relied implicitly on this model.

2. The second, a somewhat more complex direct-effects model, assumes that interrelations may exist among the psychosocial factors; the Turner and Noh[7] study is an exemplar. Interestingly, of the more than 20 studies reviewed that considered both emotional distress and life events, none considered how the two might be related.

3. The third model builds upon the second by adding sociodemographic factors into the equation. This is important because, as indicated earlier, subgroups differ with respect to their experience of social support, life events, and emotional distress (these conditions not being equally distributed across the population), and those subgroups at highest risk for stressful events may be the very ones with fewer resources available to cope with such events.

4. The fourth model extends this mediated model to include health behaviors. Health behaviors and psychosocial factors are hypothesized to interact with one another and to be associated with poor pregnancy outcomes. An example is the work by Newton and associates, in which cigarette smoking and life events were associated, with both relating to poor neonatal outcome. When controlling for smoking, the association between life events and outcome disappeared.

5. The fifth model differs from the fourth in that psychosocial factors are assumed to affect pregnancy outcome via their influence on health behavior; no direct effects of psychosocial factors are hypothesized. For example, the Harlem study found psychosocial factors not to be related to low birthweight, but to be associated with smoking and timeliness of antenatal care, which in turn influenced low birthweight.

Not only do investigators need to be explicit about what model they are testing and believe to best represent the links between pregnancy conditions and outcome, but the *shape* of the hypothesized associations must be considered. Generally, the illustrations in Figure 2, like most of our models, are cast in linear terms. At least three other curve shapes must be considered—the curvilinear, the interactive, and the weighted. With respect to life changes, a linear association would imply that a cumulative model may be operating, that is, as additional life stressors occur, they increase the probability of poor outcome accordingly. Each life event, therefore, has the same weight. A curvilinear association (depending on the shape) might suggest that a threshold model could be operating. That is, a link between life changes and poor outcomes would not be seen until a critical number of life changes had occurred. An interactive association (adding in life changes separately as well as adding in the interactions among the changes), if tested for and found, would suggest a more complex, multilevel model. That is, life changes would not be influencing pregnancy outcome in a cumulative fashion, but different events, in combination with others, would be most predictive. This is in essence the type of model

used in a few studies reviewed, although these were examining links between life events and social support, rather than different life events.[74,75] A weighted model would assign different weights to life changes, making the assumption that some events are more likely to be stressful than others; these weights would then be used, either in a cumulative, threshold, or interactive model (sociological literature suggests that links between stressful events and mental well-being are not altered appreciably by using weighted instead of unweighted sums of life events).

Implications for Prevention Strategies

The types of preventative services offered to pregnant women and the subgroups who are provided services are influenced by beliefs about the effects of social support and stress on the pregnant women. In addition, the ways in which stress and social support are thought to affect pregnancy will influence how a program is structured.

Types of services

Types of services might be different if the provider thought that psychosocial factors influenced low birthweight directly or indirectly, via health behavior. Several programs offer social support to pregnant women in the belief that support may buffer the woman from the untoward effects of stressful life events. In some cases, the implicit goal seems to be ameliorating emotional distress; in others, minimizing the effects of life changes. If interactive or buffering models are found to be applicable to low birthweight, then these strategies are likely to be effective. Other programs offer social support with the expectation that women will become more adept at managing stressful events; in other words, pregnant women are provided resources or skills in the hopes that they will learn how to obtain support for themselves, becoming less reliant on a caseworker or other support person in the health service system. The services offered by these programs are often diverse, ranging from information about pregnancy, delivery, and child care; referral services for housing; nutrition; medical care; jobs; child care; welfare; and so on.[76] In a few, specific curriculums have been developed to teach problem-solving skills, although these programs have not been used extensively for pregnant women. They have been developed more frequently for new mothers, specifically those who are disadvantaged, young, or who have a low birthweight infant.[77,78]

If, however, a program developer accepts the premise that psychosocial factors in and of themselves are less important than how these factors affect health behavior, then different strategies, or a mix of strategies, might be adopted. For example, programs attempting to bring women into antenatal health care earlier may find information on the psychosocial correlates of late entry helpful. In an extensive outreach effort to identify pregnant women not enrolled in antenatal care in Harlem, comparisons were made between women who entered the Harlem system via outreach efforts and those who came into the system through other means. The former group turned out to be more socially isolated and slightly older than the latter group.[79] In a recent paper, discussion

centers on the ways in which this information might be used to design future outreach efforts.[51] This is particularly important since the percentage of black mothers with early antenatal care did not increase in the early 1980s.[52]

The mix of services also may be affected by the ways in which psychosocial factors are thought to influence low birthweight. Most programs provide a mix of services, because (a) providers believe that multiple services are needed to alter behavior; (b) providers are unsure what services actually make a difference (given the research findings to date, this is not an unreasonable assumption); (c) providers wish to target a variety of outcomes and believe that different services are necessary for different outcomes; or (d) services often are subject to changes in funding levels and personnel complements. While appropriate in terms of offering clients a rich array of services, it is impossible to find out *what* actually makes a difference when a mix of services is provided. Few pregnancy programs allow for separation of different program components (even when randomized control designs are used, typically one group receives the enriched service package and the other does not).

Because few "strong" models exist to explain how and in what circumstances something like social support would influence women's behavior or emotional state, few programs have developed a specific detailed curriculum. Such work is being done for mothers of young children and may be relevant to pregnancy programs.[53,54,55] It is critical to collect information on what service providers actually do with their clients; process data would be welcome. Parenthetically, process data are critical in order to document changes in the delivery of a service or curriculum over time; such changes probably always occur.

Even when a particular group or community has been targeted (as is the case in most programs), it is important to document which women actually received services, or what intensity of services each woman received. In principle, most programs provide services equally to all women; however, in reality, this is probably rare. Some women have more problems, some women seem to need more support, some women more readily stay in touch with providers, and some women comply more readily with program requirements. All of these factors influence on whom the service provider focuses. How this situation affects outcome or efficacy data is not well documented.

Program Outcomes

Assumptions about stress and support influence what data are gathered. With mediated models, the outcomes over and above early labor, low birthweight, IUGR, and Apgar scores are relevant. We need to expand our outcome measures, however, to look at subgroups, and to consider long-term effects. In the Elmira Project, in which support and education were provided to rural disadvantaged pregnant women in New York, home visits were associated with reductions in smoking, preterm delivery for the smokers, and in low birthweight for the young adolescents (those under 17 years).[56] In addition, nurse-visited women were more likely to attend childbirth class and the WIC program; they also reported using social supports more frequently. Such positive outcomes may increase the chances of good child health

and development following the birth.[89] As another example, long-term effects of a supportive curriculum may be seen well after the program has ended. In a randomized trial of the efficacy of special and comprehensive prenatal services for teenagers, no effects were seen for pregnancy outcomes (as indicated by Apgar scores and low birthweight). Those young women who attended the special clinic, however, were more likely to delay their second birth than those who did not. This delay was associated with not being on welfare 17 years later.[90] Long-term effects on children (but not mothers) were seen in Project Redirection, a program for teenage mothers.[91]

Conclusion

In conclusion, the literature on psychosocial influences on pregnancy outcome, while not particularly strong, provides some clues for future research directions. More sophisticated models could be derived in order to test specifically the associations between and within psychosocial factors, sociodemographic conditions, and health behavior. Links between chronic stress and uterine contractions, and the possibility that social support could alter these associations, should be studied further. Efforts to "explain" race differentials need to take into account factors other than sociodemographic ones, to determine why these differentials are so persistent. Finally, research designs taking into account mediated effects may be useful in the design of prevention programs.

Endnotes

a. Race differentials may be accounted for in part by ethnic group variations in demographic risk factors and health behavior. Although controlling for factors such as education, age, initiation of prenatal care, smoking, and prior low birthweight births reduces race differentials, it does not totally eliminate them.[2,3,92]

b. A slightly different approach has been taken by Kramer,[93] who has attempted, via meta-analysis, to specify the proportion of variance in low birthweight and premature births accounted for by various environmental, psychosocial and medical factors.

c. Other psychosocial factors not discussed here may be relevant for an understanding of pregnancy outcome: Information seeking, relationships with mother and spouse, and self-definitions associated with motherhood are such factors. High information seeking is associated with high self-esteem; the former may act to alleviate anxiety and elevate self-esteem in the pregnant women, although this hypothesis has not been tested directly.[94,95] In addition, relationships with spouse and mother may be particularly salient during pregnancy, both as social support and, in the case of a mother, as a source of information about and role model for parenting;[96] they are associated with anxiety as well as perceptions of little support.[95,97] Women establish definitions of themselves as "mothers" during pregnancy. Pregnant women who have self-confidence as mothers and have no difficulty visualizing themselves as mothers tend to have better postpartum adjustment; they also may be less anxious, although little research has addressed this issue.[98]

d. A retrospective comparison of women who had preterm, term, and post-term deliveries suggested that mothers with pre-terms had more psychological distress with mothers with terms, who in turn had higher scores than mothers with post-terms. The authors suggest that women with post-term labors are less sensitive to oxytocin than women with pre-term or term labors.[99]

e. Almost none of the studies reviewed here report the magnitude of the associations. Typically, less than 10 percent of the variance in mental and physical health outcomes is accounted for by life events.[50,51] Possible reasons for the relatively weak associations include the

following: the importance of contextually specific facts surrounding the occurence of a negative life event, inadequacy of assessment instruments, and the role of chronic stressors rather than specific life events.[109,84] The last is particularly important in the study of pregnant women. For example, chronic stressors possibly could be a contributing factor to the race differentials in low birthweight and prematurity, over and above factors such as age of mothers, number of children, marital status, and education.[77,78]

Acknowledgment

Support was provided by the Bureau of Maternal and Child Health and the National Institute of Child Health and Human Development. The chapter was written while the author was a Visiting Scholar at the Russell Sage Foundation. The support is appreciated. Marie McCormick is to be thanked for her comments.

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Statistical Findings: Stress and Support During Pregnancy

Table 4.1
Correlates of Cigarette-Smoking in Pregnancy Among Women of Central Harlem

	Smoking Status		
	Never	Quit For Pregnancy	Current
	(*N* = 195)	(*N* = 70)	(*N* = 179)
Health Habits and Prenatal Care			
Uses alcohol	9.7	9.0	10.5
Started care on first trimester	39.9	40.8	32.1
Numer of visits > 4	86.1	87.0	78.5
Adequate care	32.6	31.1	18.7*
Stressful Events/Social Support/Mental Health			
Stressful events < 3	24.6	22.9	14.0*
Lives with husband/boyfriend	35.0	27.6	20.3*
Belongs to a church	58.6	41.7	41.7*
No situations with support	23.1	18.6	10.6*
GHQ > 5	25.1	47.1	27.4*

* $p < 0.05$, χ^2 with appropriate degrees of freedom
From McCormick, et al., present publication

Figure 4.1
Social Support and the Buffering Hypothesis

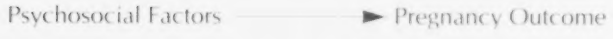
*Two points at which social support may interfere with the hypothesized causal link between stressful events and illness**

Social Support may prevent stress appraisal
Social Support may result in reappraisal, inhibition or maladjustive responses, or facilitation of adjustive counter responses
Potential stressful event(s)
Appraisal Process
Event(s) appraised as stressful
Emotionally linked physiological response or behavioral adaptation
Illness and/or illness behavior

* *From Cohen & Willis, 1985, page 313.*

Figure 4.2
Five Possible Models for Studying Associations Between Psychosocial Factors and Pregnancy Outcomes

4.2a
Direct Effects Model: Simple



4.2b
Direct Effects Model: Interrelations Among Psychosocial Factors

Figure 4.2c
Direct and Indirect Effects Model: Interrelations Among and Between Psychosocial Factors and Sociodemographic Conditions

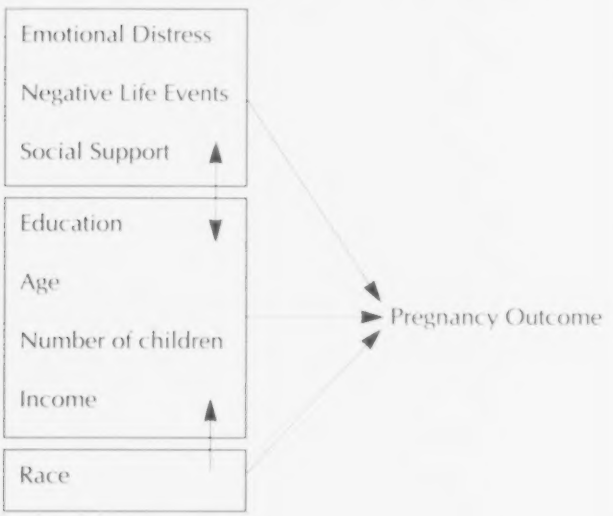


Figure 4.2d
Direct and Indirect Effects Model: Psychosocial Factors, Sociodemographic Conditions, and Health Behavior

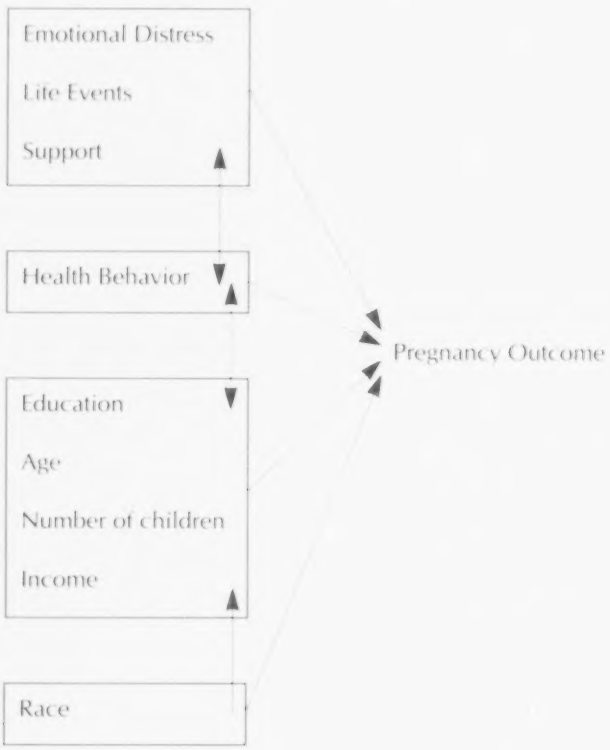
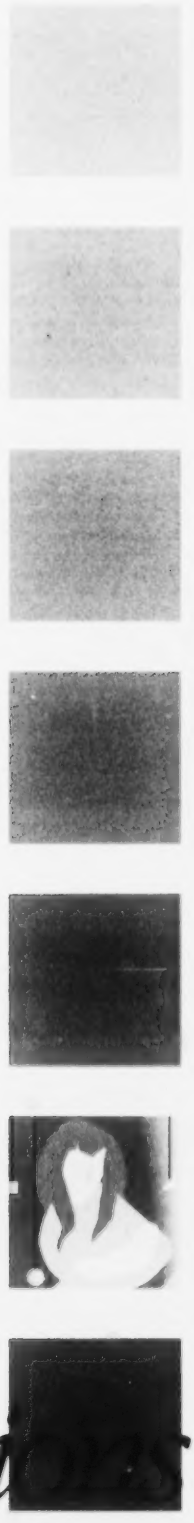


Figure 4.2e
Mediated Model: Effects Through Health Behavior

SECTION

III



Interventions

Results of a Three-Year Prospective Controlled Randomized Trial of Preterm Birth Prevention at the University of Pittsburgh

EBERHARD MUELLER-HEUBACH, M.D.

INTRODUCTION

Measures of health care in different societies are difficult to compare; however, it is often stated that infant mortality (mortality during the first year of life) is an important indicator of health care in a nation. According to the latest available statistics, the United States ranks 19th in infant mortality among the nations of the world, a decline from the rank of 15th held in 1968. Upon examination of the differences in infant mortality in different societies, it is readily apparent that by far the most important factor is neonatal mortality due to preterm delivery. In countries with lower infant mortality rates, fewer neonates die as a result of preterm delivery.[1] Thus, the causes and the

prevention of preterm birth are of utmost concern to individuals interested in perinatal health care. Definition of preterm birth as birth before completion of the 36th week is preferable to a definition by birthweight (<2500 g) because the latter includes term newborns who are growth retarded and have lower morbidity and mortality. Definition of preterm birth by gestational age is often difficult, however, due to uncertainty about the gestational age in some patients.

Prevention of preterm birth is the ultimate goal of perinatal health care, and any promising approach in this area is readily embraced, often without careful scientific scrutiny, by means of prospective randomized trials. Reports of a reduction in preterm births as a result of preterm birth prevention programs in the United States,[2] France,[3] and Martinique[4] prompted us to evaluate a preterm birth prevention program in an indigent clinic population at our institution. In contrast to the published reports, we planned to study the potential efficacy of such a program in a prospective controlled randomized design using birth before 36 completed weeks of gestation to define preterm birth.

Material and Methods

During a three-year period, all patients who registered for prenatal care at Magee-Women's Hospital in Pittsburgh were screened, and the scoring system of Creasy et al.[5] was used to assign risk scores for preterm labor and birth. A score of 10 or more placed the patient in a high-risk group for preterm labor and birth, while patients with a score below 10 were considered to be in a low-risk category. Patients who presented for the first time after 28 weeks' gestation were excluded. Similarly, patients whose estimated date of delivery was after the end of the three-year study period were not enrolled. Patients assigned to the high-risk group were approached and invited to participate in a prospective randomized controlled trial of preterm birth prevention. Participants signed a consent form approved by the Institutional Review Board. Patients who did not participate were classified as refusers if they declined participation; they were classified as ineligible if they could not be randomized before 28 weeks' gestation or if they did not return for prenatal care after randomization until they were 28 or more weeks' gestation.

Patients were randomly allocated to either a control group with the usual prenatal care or an intervention group. Two nurses with extensive obstetrical experience gave individual teaching to patients in the intervention group regarding subtle symptoms and signs of preterm labor, such as appearance of "menstrual cramps," lower back pain, "gas pain," suprapubic pressure, thigh pain, or change in vaginal discharge. The patients were instructed in self-palpation of the uterus and the contrast in feeling between a contracted and a relaxed muscle was demonstrated to them. Patients were told that they should lie down on their side when they noticed contractions and drink a quart of liquid within an hour. If contractions did not subside during this hour, patients were instructed to come to the hospital for evaluation. Weekly cervical examinations from 20 to 37 weeks' gestation were performed on patients in the intervention group, with gentle palpation of cervical effacement and dilation.

Rescreening of low-risk patients was done between 22 and 26 weeks' gestation, as well as updating of the initial risk score at other times when new findings were made.

Repeated teaching sessions were given by the investigator and the two study nurses to the resident physicians and the nurses involved in the care of clinic patients. The physicians and nurses were informed about the instructions given to patients in the intervention group in order to assure a proper response by medical personnel during communications with patients in this group.

All data concerning risk scoring, admissions for preterm labor, and deliveries were placed on special forms from which they were entered into a computer data base to permit data analysis upon completion of the study. Preterm deliveries were classified as spontaneous, indicated, or iatrogenic. Data from the Magee-Women's Hospital Perinatal Computer Data Base for an eight-month period before initiation of the study were used to establish a historic control period. Chi-squared or Fisher exact tests were used for statistical analysis.

Results

A total of 5,457 patients had initial risk scoring for preterm labor, of which 4,595 delivered at 20 or more weeks' gestation. Abortion and loss to follow-up accounted for the difference. Risk scores of > 10 (high risk) were present in 831 of the 4,595 patients (18.1%). The preterm birth rate (less than 36 completed weeks) was 10.1 percent for all patients. This rate was about 3 times higher in patients scored as being at high risk of preterm labor (21.9%) compared to patients scored as being at low risk (7.4%). The majority of patients delivering preterm (60.4%), however, were in the low-risk group. Rescreening at 22 to 26 weeks was done in 2,145 of the patients initially scored at low risk; only 33 patients (1.5%) became high risk. Six additional patients became high risk as a result of updating risk scores.

Comparison of high-risk intervention, control, refuser, and ineligible groups demonstrated similar preterm birth rates (22.1%, 22.8%, 19.5%, and 23.6%, respectively) throughout the study. There was, however, a significant decline in preterm births between the first and second years of the study (from 13.8% to 9.3%, $p < 0.001$). This decline was maintained during the third year when compared to the second year (9.3% v. 8.7%, NS). The decline in preterm births from the first to the second year was of the same magnitude in the high-risk population (-29.1%) as in the low-risk population (-32.1%). During the first year of the study, the attitude of resident physicians and nurses involved in the care of the clinic population toward the preterm birth prevention program changed from skepticism to acceptance and then to genuine interest. Being concerned about the problem of preterm birth, these health care professionals applied the instructions learned in the multiple teaching sessions to all patients under their care.

In order to verify that the decline in preterm births during the second and third years of the study was related to the preterm birth prevention program, we first examined whether the preterm birth rate during the first year of the study was exceptionally high by comparing it to the rate during the eight months before the

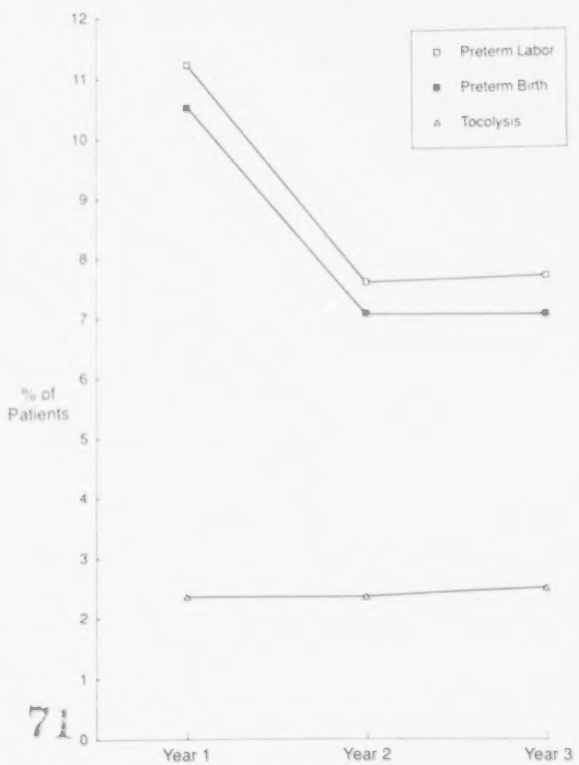
study (the historic control period). There was no significant difference in preterm birth rate between the historic control period and the first year of the study (14.1% v. 13.8%, NS).

To exclude the possibility of a time-related decrease in the preterm birth rate during the historic control period and the three years of the study unrelated to the preterm birth prevention program, we studied the preterm birth rate in the private patients who delivered at our institution and had received their prenatal care by private physicians in their offices in the area. Neither these private physicians nor their office staffs were aware of the content of the preterm birth prevention program. During the historic control period and the 3 years of the study, the preterm birth rate in the private patient population (with an average of 7,764 births per year) did not change significantly and ranged from 8.0 to 8.6 percent. When the historic control period and the first year of the study were compared with regard to preterm birth rate in clinic and private patients, the preterm birth rate was found to be significantly lower ($p < 0.001$) in the private patients. Due to the decline in preterm births in the study clinic patients during the second and third years of the study, there was no significant difference in the preterm birth rate between clinic study patients and private patients during these time periods.

We evaluated the study population (excluding patients with indicated preterm deliveries) regarding episodes of preterm labor, use of tocolysis, and prolongation of pregnancy to term in patients having received tocolysis. No case of iatrogenic preterm birth was noted in our study.

There was no significant difference between the percentage of patients presenting with preterm labor in the high-risk intervention group and those in the high-risk control group, but significantly more patients in the intervention group were candidates for tocolysis ($p = 0.01$). Nevertheless, there was no significant difference among patients receiving tocolysis with respect to prolongation of pregnancy to term. Figure 5.1 illustrates the frequency of preterm labor, preterm birth, and tocolysis in the total study population during the three years of the study. The decline in the preterm birth rate is clearly related to the fact that fewer patients presented with preterm labor during the second and third years of the study. The frequency of tocolysis was unchanged during the three years of the study. Thus, it appears that the

Table 5.1: Percentage of Patients with Preterm Labor, Preterm Birth, and Tocolysis During the Three Years of the Study



teaching and the change in attitude was associated with a decrease in the number of patients presenting with preterm labor. On the other hand, this was not accompanied by a decrease in the incidence of tocolysis, indicating that the diagnosis of preterm labor was more often made correctly by patients.

A reduction in preterm births may lead to a decrease in neonatal mortality in infants delivered before 37 weeks' gestation without congenital anomalies. There was a significant decrease in neonatal deaths in this category when the historical control period was compared to the second year of the study (from 9.1/1000 to 2.2/1000, $p = 0.0089$) and the third year of the study (from 9.1/1000 to 2.8/1000, $p = 0.0217$).

Discussion

Preterm birth prevention programs attempt to increase the awareness and recognition of subtle symptoms and signs of preterm labor among patients and their health care providers. As a result of the teaching sessions in our study, such a change became apparent during the first year of the study when health care personnel asked many questions about this program, became aware of the subtle symptoms and signs of preterm labor, and conveyed these to the patients. Patients were frequently sent to the study nurses for enrollment in the preterm birth prevention program when they, in fact, had been previously randomized into the control group. Evaluation of the preterm birth rates in our study revealed no difference between the high-risk intervention and control groups, but an overall significant decrease during the second and third years of the study irrespective of the risk assignment." Thus, the health care providers, with their concern about preterm birth, had defeated the prospective controlled randomized design of the study by also changing their care for patients who were not in the high-risk intervention group.

The initial risk scoring system classified 18.1 percent of the patients as high-risk patients, but only 39.6 percent of the preterm births occurred in the high-risk group. Conversely, a patient in the high-risk group had a 78.1 percent chance of delivering at term. Rescreening and updating of risk scores changed the initial risk score in few cases. Thus, the concept of risk scoring may either be of limited value or specific risk scoring systems need to be developed for specific populations. The results of our study suggest that educational programs applied to entire patient populations may be preferable.

It is clear that the observed decline in preterm birth rate in the study population was not a time-related trend independent of the preterm birth prevention program because comparison with the preterm birth rate in the private population during the same time period did not reveal such a trend. The decline in the preterm birth rate observed in our study may not be possible in all patient populations. In a much smaller, similarly designed study of poor, inner-city black women in Philadelphia, the investigators were not able to show any difference between high-risk control and intervention patients." This is in agreement with our findings; however, the study was not large enough to possibly document any of the changes over time which we observed in our

large, three-year study. Considering the magnitude of the problem of preterm birth, with its accompanying neonatal mortality and serious long-term morbidity (such as permanent neurological handicaps, bronchopulmonary dysplasia, and retrolental fibroplasia[8]), any promising effort to reduce the preterm birth rate should be pursued. Attempts should be made to evaluate whether a preterm birth prevention program can lower preterm birth rates in other populations with the same degree of effectiveness as it did in our indigent clinic population in Pittsburgh.

Supported by March of Dimes Grant 2-196 C-404

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Decrease and Rise in Rates of Preterm Deliveries: Haguenau Prenatal Study, 1971–1988

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Introduction

A 17-year study on the prevention of preterm deliveries in a delimited region of France has been used as an evaluation tool for the measure of effectiveness of a national policy for improving perinatal outcome (1971–1988). The same tool served as a measure of the recurrence of higher rates of preterm deliveries after this national policy was no longer followed.

This paper will describe the ways in which pregnant women have changed their behavior, coming earlier in the course of their pregnancy to the maternity outpatient clinic and more often to seek the best available prenatal care. It

was observed that the reduction in the rates of preterm births was obtained not in the high-risk categories, as was expected, but in the lower risk categories.

After cessation of the government drive, we observed how the efforts of pregnant women to come early and often to the maternity outpatient clinic were turned down, and how this resulted in the rise in the number of preterm deliveries.

Patients and Methods

The Haguenau Maternity Hospital serves a specific limited region in Alsace, France, and was used as an evaluation tool to measure the effectiveness of a policy applied nationwide. The principles of preventive measures to reduce the rates of preterm deliveries have been exposed in previous papers. They consist of a community-based intervention proposing to all pregnant women a new type of prenatal care. The major components of the intervention are a risk analysis for individual factors predicting a preterm delivery,[1] and several measures aimed at decreasing uterine contractions and preterm deliveries, which have been described in detail elsewhere.[2]

The basis for applying this policy was a government program approved for five years in 1971, and extended for five additional years in 1976. The objectives were to reduce perinatal accidents leading to death and perinatal-induced handicapping conditions. The means employed included financial inducements for the public hospitals to help improve their equipment for delivery and neonatal care; financial inducements for postgraduate training sessions for doctors, midwives, and nurses working in the field; and financial inducements to speed up public information directed at women to encourage better perinatal follow-up.

This government initiative helped in spreading basic concepts and techniques for the improvement of prenatal and intrapartum care, and neonatal resuscitation measures as well as neonatal care. In addition, the drive helped in spreading new ideas, such as the prevention of preterm delivery using techniques we proposed.

After 1981, a new government took over and decided not to pursue this established policy. As good results had been achieved, the opinion of the politicians was that the program had served its purpose and that no supplementary efforts were needed to maintain the ongoing measures. Thus, perinatalogy came to be out of fashion, and public attention was drawn to other aspects of reproduction, specifically to questions centered around in utero fertilization in the early 1980s and to AIDS in the late 1980s.

In the present study, we measure the knowledge and conviction of pregnant women to use the best accessible prenatal care system provided free of cost at the outpatient clinic of the Haguenau Maternity Hospital; specifically, the proportion of women consulting in the first trimester (instead of being followed by their general practitioner) and the number of prenatal visits made before 26 weeks.

Information about the women and their pregnancies was very carefully gathered using the best knowledge available by the last menstrual period (LMP), length of cycle, ultrasound scan, and pediatric examination of the neonate. All of the data were computed in the days following delivery. All babies transferred to a

neonatal intensive care unit were included in the study, as well as babies of women transferred to a referral center.

Results

The results were examined for two successive policy application periods. The first sequence, from 1971 to 1982, was divided into three periods of four years each. The second sequence will show the last period of four years, from 1983 to 1986.

Reduction in preterm deliveries

A progressive reduction in preterm deliveries was observed during the 12-year period from 1971 to 1982. The global rate of preterm births defined as less than 37 weeks of gestation from the first day of the last menstrual period was reduced from 1971 to 1974 and from 1979 to 1982 (see table 6.1).

Reduction in transfers to a neonatal intensive care unit

As the number of babies in need of intensive care had decreased, the transferral to a neonatal intensive care unit because of preterm birth was significantly reduced (see table 6.2). It should be noted, however, that the proportion of transferred babies to the number of preterm births was not reduced but rather increased. In the same period, transfers for other reasons and, specifically, for malformation of the newborn were augmented.

Reduction in length of hospitalization required by preterm newborns

The need for intensive care for preterm newborns has been quantified according to the number of days of hospitalization required for the babies transferred to a Level III center neonatal intensive care unit (NICU) in Strasbourg as well as to the neonatal care unit in the local hospital of Haguenau (see table 6.3).

Reduction in neonatal mortality

Neonatal mortality was reduced in this time sequence, and the decrease in the number of preterm babies was a part of this reduction. Table 6.4 describes the total neonatal mortality in the three successive time periods. A direct standardization was done, as if the proportion of preterm births would not have changed from that of the first period (1971–1974), with week-specific mortality rates for 1971 to 1978 and for 1979 to 1982. This shows that about half of the progress can be attributed to an improvement in the care of newborns and that half of the progress can be explained by the reduction in the number of preterm babies. The total reduction of neonatal deaths was then obtained by better care as well as "better babies."

Reduction in preterm births in women with no defined risk factors

The reduction in preterm births was not obtained in high-risk women; that is, those women with a previous preterm birth, with a previous stillbirth, of short stature, of less than average weight, of less than 21 years, of more than 35 years, or with a history of bleeding in the second or third trimester. On the other hand, a significant reduction in preterm births was observed when the women did not fall in the above-mentioned risk group. Thus, fewer preterm births were observed in those women characterized by the absence of a defined risk

factor; that is, with no previous preterm birth, with no previous stillbirth (among parous women), with a normal stature (above 152 cm), with a normal prepregnancy weight (more than 48 kg), of between 24 and 34 years of age, and with no history of bleeding in the second or third trimester (see table 6.5).

Reduction in high-risk factors

The rate of high-risk factors was reduced in the observed population. This reduction was observed for previous preterm birth, for age less than 21 years and more than 35 years, and for bleeding in the second or third trimester (see table 6.6). The relationship between this reduction in risk factors and the population of pregnant women will be discussed subsequently.

Early obstetrical prenatal care and prevention of preterm deliveries

Our hypothesis was that a new type of prenatal care could prevent preterm deliveries. The basic premise was that a reduction in job-related and home-related excessive physical efforts for at-risk women would be effective. That meant that women had to be convinced to come early and often to meet the teams of obstetricians and midwives able to inform them and offer specific risk assessments for each woman at each prenatal visit.

The pregnant women had to be convinced to come early and often to meet these new proposals. Then the early enrollment in the obstetrical outpatient clinic and the number of prenatal visits before the end of the 6th month could serve as accurate measures of the acceptance of this care proposal and of the effectiveness of the information given to the general public and to all women. We used these simple measurements as markers of the success of the government efforts in the prevention of preterm births.

Table 6.7 and figure 6.1 show the relationship between earliness of care and preterm deliveries for four-year periods and for three groups of women defined by the number of years of school completed (Up to 9 years, 10–12 years, and 13 years and above). The acceptance measures here described are:

A. The mean number of prenatal visits in the first two trimesters of pregnancy at the outpatient clinic of the obstetrical department;

B. The proportion of women in each group enrolled in this outpatient clinic;

C. The proportion of pregnant women in each group who never had a prenatal visit at this outpatient clinic of the obstetrical department; and

D. The proportion of preterm deliveries (by group and by study period).

The new type of prenatal care was accepted and was requested by all groups of women, with important differences between groups. The more informed the women were, the earlier they came in. For the first 12 years of study, from 1971 to 1982, a progressive rise in acceptance of care was noted, with persistent differences between groups, and with a time lag of about four years between women with 13 years of schooling and women with 10–12 years, and a time lag of eight years between women with 13 years of schooling and women with up to nine years. In the meantime, during this period of progressive acceptance of prenatal care, the rate of preterm deliveries went down, with per-

sistent differences between groups, and also with a time lag difference between groups of the same order as that observed on the behavior of acceptance of new care. After 12 years, in the fourth period (1983–1986), instead of improvement, a new movement of reduction of the three measures was observed. The pregnant women sought consultation much later in the course of their pregnancies and came less often in the first two trimesters. In addition, more women came in directly for delivery without being previously followed. During the same period, the rates of preterm deliveries went up for the three observed groups of women.

Mathematical relationship between prenatal care and preterm deliveries

A regression analysis was done to measure the precise relationships between the preceding characteristics of prenatal care and the outcome in terms of the proportion of preterm births. The regression curve for women by group and number of preterm deliveries is shown in figure 6.1, with the equation Y (proportion of preterm births) = X (proportion of pregnant women by school attendance group enrolled in prenatal care at the outpatient clinic of the maternity hospital in the first trimester).

$Y = 0.078–0.074X$

$r = -0.95$

$p = 0.001$

A similar relationship was found between the number of prenatal units at the outpatient clinic of the maternity hospital and the number of preterm births, and a similar correlation was found between the proportion of women not followed by the obstetrical team and the number of preterm births.

Discussion

The observed mathematical relationship between the characteristics of care and outcome are very similar to a dose-effect relationship. This feature supports the hypothesis of a causal relationship between this type of care and the observed effect. This point is important, as our policy has been applied in the whole of France, and without the opportunity to apply an experimental design, as we would like, to support a demonstration of the effectiveness of our policy. On the other hand, we know the effort to prevent preterm deliveries has been applied in France, but has not been applied in Germany, the United Kingdom, or the United States. It happens that France is the only country among these four to have observed a reduction in preterm births between 1970 and 1980, and, during this same period, no reduction could be demonstrated in the three other countries. Obviously, this is not as good a demonstration as a randomized trial would have been; however, this difference cannot be discarded.

We did not expect that France, by itself, could serve as a control. But the cessation of the national policy in the perinatal field in 1981 has provided us with this quasi-experimental design. We can take advantage of this to propose a new argument for a causal relationship between the new type of care and prevention of preterm deliveries, as the numbers were exactly the same on the regression curve backup.

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Statistical Findings: Decrease and Rise in Rates of Preterm Deliveries Haguenau Prenatal Study 1971–1988

Table 6.1
Preterm Deliveries and Live Births

	1971–74	1975–78	1979–82	*P* Value
< 32 weeks	5.4 299/5548	4.0 192/4787	3.6 210/5811	0.001
35–36 weeks	2.9 159/5548	2.1 102/4787	2.4 142/5811	N.S.
33–34 weeks	1.1 59/5548	0.8 39/4787	0.7 39/5811	0.05
< 33 weeks	1.5 81/5548	1.0 51/4787	0.5 29/5811	0.001

Reduction of preterm births (live-birth) by time period and by duration of gestation since last LMP. The observed reduction in preterm births is of one birth for the total preterm figures, and is one half for the most dangerous preterm births (less than 33 weeks).

Table 6.2
Transfers to a Neonatal Intensive Care Unit

	1971–74	1975–78	1979–82
33 weeks	38/81	27/51	12/29
33–36 weeks	15/218	17/141	17/181
≥ 37 weeks	58/5548	17/4787	22/5811

The numbers of transfered babies were significantly reduced for term babies as well as for the less than 33 weeks birth babies. The proportion of transfers compared to preterm birth was not reduced, the reduction was only possible by the decrease in early preterm births.
Numbers of days of stay in the intensive care unit (at Strasbourg referral center) or in the neonatal pediatric ward in Haguenau hospital for babies born before 35 weeks, after exclusion of hospitalizations due to a malformation as the major cause (for 1,000 births).

Table 6.3
Days of Hospitalization Related to Preterm Delivery

	1971–74	1975–78	1979–82	*P* Value
NICU Strasbourg	425	296	182	0.001
Neonatal pediatric ward Haguenau	437	320	223	0.001

The number of days needed for hospitalization related to preterm delivery was significantly reduced for transfered babies to a NICU and to the local pediatric ward.

Table 6.4
Neonatal Deaths Per Thousand Live Births

	1971–74	1975–78	1979–82	*P* Value
0/00	8.3 46/5548	6.5 31/4787	3.1 18/5811	0.001
Standardized rates and confidence interval	8.3	7.9 48/96	5.0 30/76	

The upper line shows the observed figures of neonatal deaths among live births by study period. The lower line depicts the figures obtained after standardization, as if the distribution of births by gestional age would not have changed in the second or third study periods, and with week-specific mortality rates of these specific periods.

Table 6.5
Rates of Preterm Births, by Risk Factor, by Period

	1971–74	1975–78	1979–82	*P* Value
Previous preterm	12.7 52/408	12.5 31/248	12.3 33/269	4–5
No previous preterm	4.3 124/2868	3.2 71/2247	2.9 88/3008	0.01
Previous still-born	10.8 7/65	13.2 7/53	8.9 7/79	N.S.
No previous still-born	5.3 169/3211	3.9 95/2442	3.6 114/3198	0.001
Height < 1.52 m	8.2 19/232	7.8 17/219	6.3 16/252	N.S.
Height ≥ 1.52 m	5.6 272/4871	4.0 179/4439	3.8 209/5478	0.001
Weight < 48 kg	7.5 50/668	5.4 35/645	5.3 41/777	
Weight ≥ 48 kg	5.5 245/4489	4.2 164/3944	3.8 186/4950	0.001

Table 6.6
Rates of Preterm Births, When a Risk Factor was Observed or Not Observed

	1971–74	1975–78	1979–82	*P* Value
Age less than 21 years	7.3 70/961	6.5 52/801	6.0 49/806	N.S.
21–35 years	5.4 217/4172	3.9 146/3770	3.6 177/4851	0.001
≥ 36 years	6.7 31/461	5.5 10/181	5.6 10/180	N.S
Bleeding in second trimester				
yes	18.2 27/148	20.6 20/97	14.3 18/126	N.S
no	6.2 120/1931	3.9 108/2804	3.8 164/4371	0.001
Bleeding in third trimester				
yes	17.1 24/140	11.8 8/68	23.0 10/87	N.S
no	5.3 179/3392	4.0 159/3967	3.6 194/5429	0.001

Table 6.7
Rate of High-Risk Factors Among Pregnant Women by Study Period

	1971–74	1975–78	1979–82	*P* Value
Previous preterm	12.5 428/3418	10.0 259/2604	8.3 280/3357	0.001
Previous stillbirth	2.0 69/3418	2.1 54/2604	2.4 81/3357	N.S
Height 152 cm	4.6 242/5292	4.9 236/4807	4.5 263/5819	N.S
Height 48 cm	12.9 688/5336	14.1 664/4721	13.6 790/5818	N.S
Age 21 years	17.4 1014/8811	17.1 841/4918	14.1 839/5948	0.001
Age 35 years	8.4 488/5811	4.0 196/4915	3.1 187/5948	0.001
Bleeding 2nd trimester	7.1 151/2134	3.3 99/2961	2.8 126/4514	0.001
Bleeding 3rd trimester	3.9 143/3630	1.7 71/4122	1.6 88/5572	0.001

Table 6.8
Change in Prenatal Care and Preterm Birth Rate According to Parental Educational Level

	School attendance	1971–74	1975–78	1979–82	1983–86	*P* Value
N	1	2794	2975	3806	2984	
	2	1965	1640	1725	2109	
	3	282	377	433	475	
A	1	0.9	1.8	2.3	2.3	0.001
	2	1.5	3.0	3.5	2.8	0.001
	3	2.2	3.8	3.8	3.1	0.001
B	1	17.7	28.4	38.6	37.5	0.001
	2	30.0	49.5	61.6	48.4	0.001
	3	47.5	65.5	69.5	55.2	0.001
C	1	46.2	23.9	8.6	18.8	0.001
	2	27.7	8.8	3.6	20.7	0.001
	3	10.6	4.0	0.9	17.3	0.001
D	1	6.8	5.0	4.5	5.2	0.001
	2	5.6	3.5	3.3	4.3	0.01
	3	3.7	2.7	2.5	3.6	N.S.

N : numbers of pregnant women by school attendance group

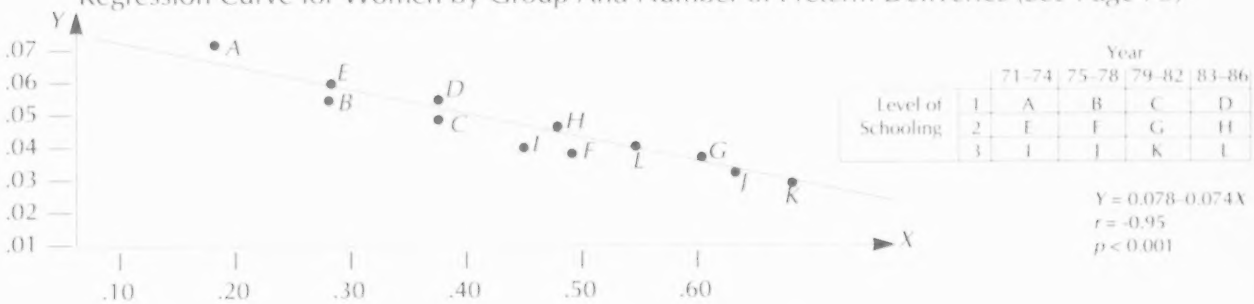
A : mean number of prenatal visits at the out patient clinic of the obstetrical department.

B : proportion of pregnant women enrolled at the out patient clinic of the obstetrical department.

C : proportion of pregnant women not followed at the obstetrical department.

D : rates of preterm births by group and by period.

Figure 6.1
Regression Curve for Women by Group And Number of Preterm Deliveries *(See Page 73)*



The West Los Angeles Prematurity Prevention Project: A Progress Report

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Introduction

During the 1970s, the United States observed a dramatic reduction in perinatal morbidity and mortality. On the other hand, the incidence of low birthweight (LBW) births during this period decreased only 11 percent (approximately 1% per year).[1] Thus, the technological advances in obstetrical and neonatal care, which were thought to impact morbidity and mortality, did not significantly influence the incidence of LBW. Since prematurity, a major component of the low birthweight problem, is now the leading cause of poor

pregnancy outcome, we must begin to develop strategies for prevention.

Beginning in 1970, we collected baseline data from the west area of Los Angeles County to identify pregnancy-related problems. Using these data, we developed a risk scoring system, which was global in design, to identify pregnancies at risk for neonatal morbidity and mortality.[2] Between 1975 and 1979, our experiences helped us recognize that our global approach to risk assessment needed to be redefined and directed toward identifying patients at risk for specific problems, such as preterm birth, intrauterine growth retardation, diabetes, and hypertension.[3] Thus, over time we developed a strategy of prenatal care based on levels of risk, with special attention given to the prevention of specific problems.

Guidelines for the implementation of programs for the prevention of preterm birth came from two sources: (1) A risk assessment system, described by Papiernik in 1969, which formed the basis for identifying patients at risk and for developing prevention strategies;[4] and (2) preliminary data subsequently published by Herron et al. in 1982, which described the content of a program thought to significantly reduce the incidence of prematurity.[5]

These preliminary data generated tremendous interest in the prevention of prematurity in the United States. Coupling these guidelines and this interest, we developed a project for studying prematurity prevention in our patients at risk. The following provides a progress report on that project.

Development of a Prevention Project

We believe that a prematurity prevention program should include three major components.

Prenatal Care System

A well-organized prenatal care system is an absolute requirement for a prematurity prevention program. A new program encouraging a different philosophy and a change in provider behavior will not be successful unless the system is prepared to provide a different type of prenatal care from that customarily provided in America.

Risk Assessment System

A task force was established in 1978 by the World Health Organization to set forth guidelines for developing risk assessment systems for maternal and child health.[6] This task force recommended that risk assessment systems should be developed from and tested on the population to which they are to be applied prior to beginning intervention programs. The process is as follows: First, a risk assessment system is developed from retrospectively collected data and its sensitivity and specificity is determined. Next, the risk assessment system is applied prospectively to validate its sensitivity and specificity. The final step is to test the scoring system in a prospective type intervention study using a control population to again test the scoring system's sensitivity and specificity. Most risk assessment systems have not been properly designed and tested prior to instituting intervention strategies.

Data System

An important component of our prevention project is our ability to manage the large

amounts of data gathered from each patient. The source document for our program is the POPRAS (Problem Oriented Perinatal Risk Assessment System) perinatal record.[7] Using the POPRAS record, we have developed an online interactive computerized network referred to as PIDS (POPRAS Interactive Data System). This network links our west Los Angeles prenatal clinics with the scientific data center located at Cedars–Sinai Medical Center, our project headquarters, and the Harbor–UCLA Medical Center. This system provides us with the following:

1. Computerized risk assessment;
2. A randomization scheme for assignment of intervention protocol;
3. An appointment scheduling system;
4. Patient tracking and compliance checks;
5. Real-time reports;
6. Online hospital data management; and
7. Rapid turnaround data management and analysis.

Funding a Prevention Project

This project is funded by the Maternal and Child Health Branch of the state of California.

Study Design

We were initially confronted with the task of determining what types of interventions should be tested for preventing preterm birth. Our review of the literature suggested that the etiology of prematurity is most likely multifactorial, yet stress appeared to be a central issue. In 1984, we had proposed a hypothesis for the etiology of preterm labor where stress was felt to be a predisposing condition.[8] We therefore directed our attention toward interventions which reduced stress and interventions which promoted the maintenance of pregnancy. This approach was in concert with the interventions used by Papiernik.

For our prematurity prevention project, we decided to test five treatment protocols for high-risk women. The precise study design algorithm was previously published.[7] The intervention protocols selected were bed rest, psychosocial support, and an oral progestin (Provera) matched with a placebo and a control (education and nutrition only).

Description of Project

The patients' risk status is determined using the PIDS program. Patients who have one or more selected high-risk factors are considered high-risk patients and are randomized into one of the five interventions.[7] In addition to standard risk assessment, a detailed psychosocial history is taken but not used in the assessment of risk.

All high-risk patients receive education about preterm labor, signs and symptoms, what actions to take if symptoms occur, and a class detailing what to expect in the hospital. In addition, all patients receive extensive nutrition counseling and support. Most patients deliver at Harbor–UCLA Medical Center and their data

are entered into the data system by labor and delivery room nurses or data entry clerks.

The Preliminary Results

Preliminary results from 4,034 total deliveries occurring between January 1, 1979, and June 30, 1986, are presented in table 7.1. These data were previously published in abstract form.[11] The importance of these preliminary results is to recognize that during the early phase of our study we had an apparent impact on the incidence of preterm deliveries, especially those with very low birthweight infants (< 1500 g). The very low birthweight infants are the most costly to care for and account for the majority of preterm infants who are left with disabilities or handicaps.

In addition, a preliminary analysis has been carried out to assess the association of psychosocial stress with prematurity. This has also been published in abstract form.[12] In a retrospective study of 359 women with preterm deliveries matched with a group of women delivering at term, 4 factors were found to be significantly associated with preterm birth (see table 7.2). In our prospective study from 1 January 1979 to 30 June 1986, only three factors were determined to be significantly associated with preterm birth (see table 7.2). These preliminary results suggest that there may be certain psychosocial factors which could be used to facilitate the identification of patients at risk for preterm birth.

Summary and Future Direction

As of May 1988, the West Area Los Angeles Prematurity Prevention Demonstration Project is well established and has completed its fifth year of operation. The strategy of risk assessment, randomized application of specific interventions, and computerized monitoring to

Table 7.1
West Los Angeles Prematurity Prevention Project Preliminary Data

	Baseline Prematurity Rate (percentage)		Study Prematurity Rate (percentage)* (4,034 patients)			
	< 37 Completed Weeks of Gestation				< 31 Completed Weeks of Gestation	
	1979–1982 (8,249 patients)	1982–1983 (3,108 patients)	Control Clinics	Experimental Clinics	Control Clinics	Experimental Clinics
High Risk	11.24	9.92	8.54	5.70†	1.02	0.61‡
Low Risk	5.04	4.58	4.77	5.53	0.41	0.40

* *Data as of 6/30/86.*

† *49% decrease compared with 1979–82 baseline.*
43% increase compared with 1982–83 baseline.
33% increased compared with Control Clinics ($p = .05$).

‡ *40% decrease compared with Control Clinics.*

assess their impact on preterm birth appears promising for providing new information to facilitate our understanding of the problems of preterm birth.

Randomization of high-risk patients to specific interventions will be completed as of 31 December 1988, and the project will end by July 1989, at which time all patients entered into the study will have delivered. At that time, a final analysis of the overall effect of the project, as well as the effect of each specific intervention, will be determined. In addition, an important part of the final analysis will include validation of our risk assessment screening tool in the control population to determine whether it has maintained its original sensitivity and specificity. Since psychosocial risk factors were not originally included in our risk assessment model, we will test the inclusion of certain of these factors into our scoring system to determine whether they would improve the sensitivity and specificity of our original tool.

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Table 7.2
Psychosocial Risk Factors Associated with Preterm Birth

Retrospective Study (Preliminary Results)

1. Mother working throughout pregnancy;
2. Patient not living with the baby's father;
3. Perceived problem or crisis near delivery; and
4. Perceived excessive stress during pregnancy.

Prospective Study (Preliminary Results)

1. Mother born in the United States;
2. Patient having had thoughts of hurting self or unborn baby; and
3. Patient having a close family member die during pregnancy.

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The South Carolina Multicentered Randomized Controlled Trial to Reduce Low Birthweight

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Introduction

South Carolina has one of the highest low birthweight rates (LBWR, < 2500 g) and very low birthweight rates (VLBWR, < 1500 g) in the United States.[1] This dubious distinction contributes heavily to the state's excessive infant mortality rate, also one of the highest in the nation.[2]

As other causes of infant mortality decrease, low birthweight assumes greater importance. In the United States, the LBWR is 7 percent and accounts for 80 percent of the infant deaths.[3] Very low birthweight rates have not changed significantly in the last 20 years.[4]

These small infants are not only at high risk for dying, but also for long-term morbidity, such as cerebral palsy and other neurological deficits.[3]

Several investigators have described interventions to reduce preterm birth (< 37 completed weeks' gestation) and low birthweight with inconsistent results.[4-7] This paper reports on a multicentered randomized controlled trial (RCT) of an intervention used in an attempt to reduce the LBWR in a group of women identified as being at increased risk for this poor perinatal outcome.

Experience with two previous South Carolina programs provided the basis for the hypothesis tested in this study. One program used nurse-midwives in the adolescent clinics of the Medical University of South Carolina (MUSC) to provide high-quality, comprehensive prenatal care to adolescents. This program, although not an RCT, reported a reduction of the LBWR in these young women.[8] The other program used public health nurses to successfully screen for high-risk patients in the statewide high-risk perinatal program.[9] The stated hypothesis was that the low birthweight rate in the intervention group would be less than the LBWR in the control group.

Methods

Study Population

Women who attended state-funded prenatal clinics were eligible for randomization if they had a score of 10 points or greater on a scoring system using the risk factors of Papiernik,[10] later modified by Creasy.[11] Public health nurses in prenatal and the Special Supplemental Food Program for Women, Infants and Children (WIC) clinics administered the scoring index after being trained in its use. In addition, women who had a low birthweight infant in their last pregnancy were eligible for randomization. All women randomized had to be free of known medical or pregnancy complications (i.e., hypertension, diabetes, renal disease, or multiple pregnancy). Women with these complications were eligible for the statewide high-risk medical program and were not randomized. If a randomized woman developed any of these complications during the index pregnancy, she continued in the study and also received treatment from an obstetrician for the complications.

Random Allocation

A list of computer-generated randomized numbers was sealed in sequentially numbered opaque envelopes. Upon identification of an eligible patient in the clinic, a central telephone number was called and the next envelope was chosen by a lay administrator not involved in patient care. Patients were assigned to attend either a separate low birthweight prevention clinic (study group) or to attend the regular high-risk obstetrical clinic (control group). Both groups had access to the WIC program, nutri-

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tionists, public health nurses, and complete funding for prenatal care by the state health department. All women received intrapartum care by obstetricians at the five regional centers collaborating in the trial.

Sample Size

From the beginning of the study, it was felt that it would be essential to pay for the prenatal care of both the program and control patients. Funds were made available from multiple sources (e.g., the Jobs Bill, the Department of Health and Environmental Control, and the March of Dimes) for support of approximately 1,600 total patients. The sample size necessary to detect a change from a LBWR of 13% (the estimated low birthweight rate of the high-risk group) to 8% (the state LBWR) at $p \leq .05$ with a power of 90 was calculated to be 1,546 patients. The sample size determination to test a similar hypothesis for the VLBWR exceeded projected resources. The original sample size of 1,546 was, however, reduced to 1,435 women due to limited resources extended over a prolonged period of time.

Intervention

As soon as possible after randomization (within three weeks), the women in the program group were seen in the low birthweight prevention clinic. An initial hour-long, one-on-one teaching session identified the women's specific risks with careful analysis of lifestyle behaviors, including substance abuse, nutrition status, stress, level of activity, and social support. Patients were taught to recognize the subtle signs and symptoms of preterm labor and to palpate for contractions. They were given the phone number of the low birthweight clinic nurse and the labor room and encouraged to call with any problem. The return visits lasted 20–30 minutes, with a review of all the initial teaching done each time. The same nurses or nurse-midwives saw the patient at one- to two-week intervals throughout the pregnancy. A gentle cervical exam to monitor possible cervical change was done at each visit, with care taken not to enter the endocervical canal. Recommendations to decrease physical activity were based on the information gathered during the visits.

Intensive follow-up was done by the nurses nurse-midwives on women who had missed appointments. The assistant study director made quarterly site visits to each of the centers to review charts and monitor adherence to the protocol. Case loads were assessed to ensure that the time allotted for each patient was adequate to maintain the protocol. In addition, staff from all five regional centers met quarterly to discuss problems and receive feedback on data collection but without knowledge of perinatal outcomes in either the program or control group.

Consent

The Institutional Review Board of the Medical University of South Carolina determined that no formal consent was necessary for women to enter the study since there was no unusual or hazardous risk involved in prenatal care given in either group.

Interim Analysis

After accumulating 800 pregnancy outcomes, an interim analysis was conducted by a

team of three investigators who were not directly involved in the clinical management of the trial. All were independent of the study and the institutions associated with it. The data review group met in Atlanta on 26 March 1986, together with the principal investigator of the study and two consultants from the Centers for Disease Control.

The analysis concentrated on live births since they represented the denominator of the low birthweight rate, which was the measure used in the hypothesis. The predictive power of the screening tool for low birthweight and very low birthweight was two to three times higher than for U.S. population rates. There was essentially no difference in the low birthweight rate between the groups. Similarly, the mean birthweight did not differ. The proportion of live births with birthweight less than 1500 g, however, was 2.1 percent in the program group versus 4.2 percent in the control group. The apparent effect of the program was to shift births from the very low birthweight to the moderately low birthweight group, with no apparent shift from the moderately low birthweight group into the normal birthweight group. The data review group concluded that there were no reasons for stopping the trial, encouraged its continuation, and kept their report confidential from the project staff.

Results

The trial began on 1 July 1983, and ended on 31 October 1987. During this period, 1,458 women were randomized, 728 to the program and 730 to the control group (see figure 8.1). A total of 17 women had multiple gestation, 11 in the program and 6 in the control group. Six women were not pregnant, three in each group. Of the remaining 1,435 singleton pregnancies, 34 resulted in abortions (22 program and 12 control). There were 13 fetal deaths (3 program and 10 control). Forty-two patients were lost to follow-up (22 program and 20 control). All of the above women were excluded from analysis either because they did not have a live singleton birth or because the outcome of their pregnancy was unknown. All exclusions were validated by a blinded observer not connected with the study. The profile of the exclusions does not vary significantly with the profile of those women included in the analysis (see table 8.1).

A total of 1,346 women with live births and known outcome, 667 in the program group and 679 in the control group, were included in the reported analysis. The randomization process achieved comparability between groups for maternal race, education (in years), marital status, age (in years), risk scores, gravidity, and gestational age at randomization at clinic sites (see table 8.2). Nearly one-third of the patients were less than 16 gestational weeks when randomized. Randomization of the patients to the program and control occurred evenly within each hospital. One site (MUSC) accounted for 36 percent of the patients (see table 8.3).

The group birthweight distribution for both the program and the control groups is presented in table 8.4. There were no statistically significant differences, either in the very low birthweight rate or in the low birthweight rate, between program and control patients. The odds ratio for program versus control patients

for LBW was 1.09 (95% CL, 0.8 –1.4), and for VLBW was 1.15 (95% CL, 0.7–2.0).

Race was not considered in the hypothesis, but interest as to whether intervention may have affected risk groups differently led to an analysis by risk category and race. This post-hoc analysis suggested that black program women with a risk score of 10 or more had a statistically significant lower very low birthweight rate than black control women (see table 8.5). When the risk group[10+10] was examined, no significant difference occurred in gestational age for either the total population or for any one particular race (see table 8.5).

Discussion

This randomized controlled trial with patients in public health clinics demonstrated little change in the low birthweight rate. Effective interventions have been reported in some patient populations, but have not been replicated by other investigators. Thus, it is becoming apparent that low birthweight prevention programs involving risk assessments which target specific populations for interventions do not benefit all populations to the same degree. It appears that the importance of specific risk factors for low birthweight and their corresponding intervention may depend on the population studied.

Papiernik first claimed benefit from assessment and early intervention in France[14] with education, cervical check, cerclage, and/or tocolysis. Creasy modified Papiernik's risk factors in the pilot study in California.[15] Papiernik[16] has also demonstrated general improvement and acceptance of low birthweight prevention programs by social class of the patient.

Main et al.,[16] in a randomized controlled trial with inner-city patients, failed to detect any increase in gestational duration, but their study had a very small sample size (60 patients in each group). They subsequently reported disappointment in the lack of sensitivity and specificity in efforts to validate Creasy's scoring system.[17]

Moore described an educational program for doctors and patients with much more success in private patients, but little change detected in results in public health programs for less advantaged women.[18] Meis and Moore reported the etiology of preterm labor in the patient population to be a factor in the success of their prevention program.[19]

The value of social support in improving perinatal outcomes has been the subject of studies by Oakley[20] and Spencer.[21]. Differences in birthweight were found in South Carolina in a case control study of social support using a resource mother favoring this kind of social support.[22]

In a state where the access to and availability of prenatal care for indigent women at risk for low birthweight outcomes is an increasing concern, this study provides important insight as to the future direction that research should take. It appears from this RCT that nurses/nurse-midwives may have provided prenatal care to a high-risk population with comparable results, rather than better results (as stated in the original hypothesis) when compared to outcomes of women provided care by obstetricians in high-risk clinics. This hypothesis should be tested in a future study. The sample

size necessary to test this hypothesis is not prohibitive and the study would provide important public health information.

The trend of black women in the program group to do better than black women in the control group is even more encouraging because it suggests that some component of their persistently higher low birthweight rate may be more amenable to this intervention than their white counterparts. This observation, however, was not in the original hypothesis, and needs to be studied specifically by repeating this RCT with that as the stated hypothesis. Possibly the difference in low birthweight very low birthweight by race was related to access to quality prenatal care. Greenberg[4] noted a greater effect of prenatal care in those patients at greatest socioeconomic risk. Korenbrot[5] reported a trend toward lowering of the low birthweight and very low birthweight rates with a package of quality care.

The unchanging rates of low birthweight preterm births should be recognized as a very serious maternal and child health problem. Despite improvements in infant mortality, the United States compares unfavorably with developed nations.[2] Our birthweight-specific mortality (i.e., survival within birthweight groups), however, ranks with the best in the world.[2]

Intensive care crisis intervention is seen as the pinnacle of our achievement and a measure of our success. Lost from sight is the fact that the neonatal intensive care unit (NICU) should serve as a backup adjunct to prevention. One should not let the previous strides made in technological and expensive treatment overshadow the small but important steps that can be made toward prevention. The expense associated with mounting further research is minimal compared to the savings in human and financial terms if a 50 percent reduction in the VLBWR is potentially achievable.

Acknowledgments

The authors wish to acknowledge the encouragement and scientific advice of Ian Chalmers, Director, National Perinatal Epidemiology Unit, Oxford, England. We also wish to express our gratitude to the March of Dimes, the South Carolina Department of Health and Environmental Control, and the Robert Wood Johnson Foundation for their support of this report.

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Statistical Findings: The South Carolina Multicentered Randomized Controlled Trial to Reduce Low Birthweight

Figure 8.1
The South Carolina Multicentered Randomized Controlled Trial to Reduce Low Birthweight

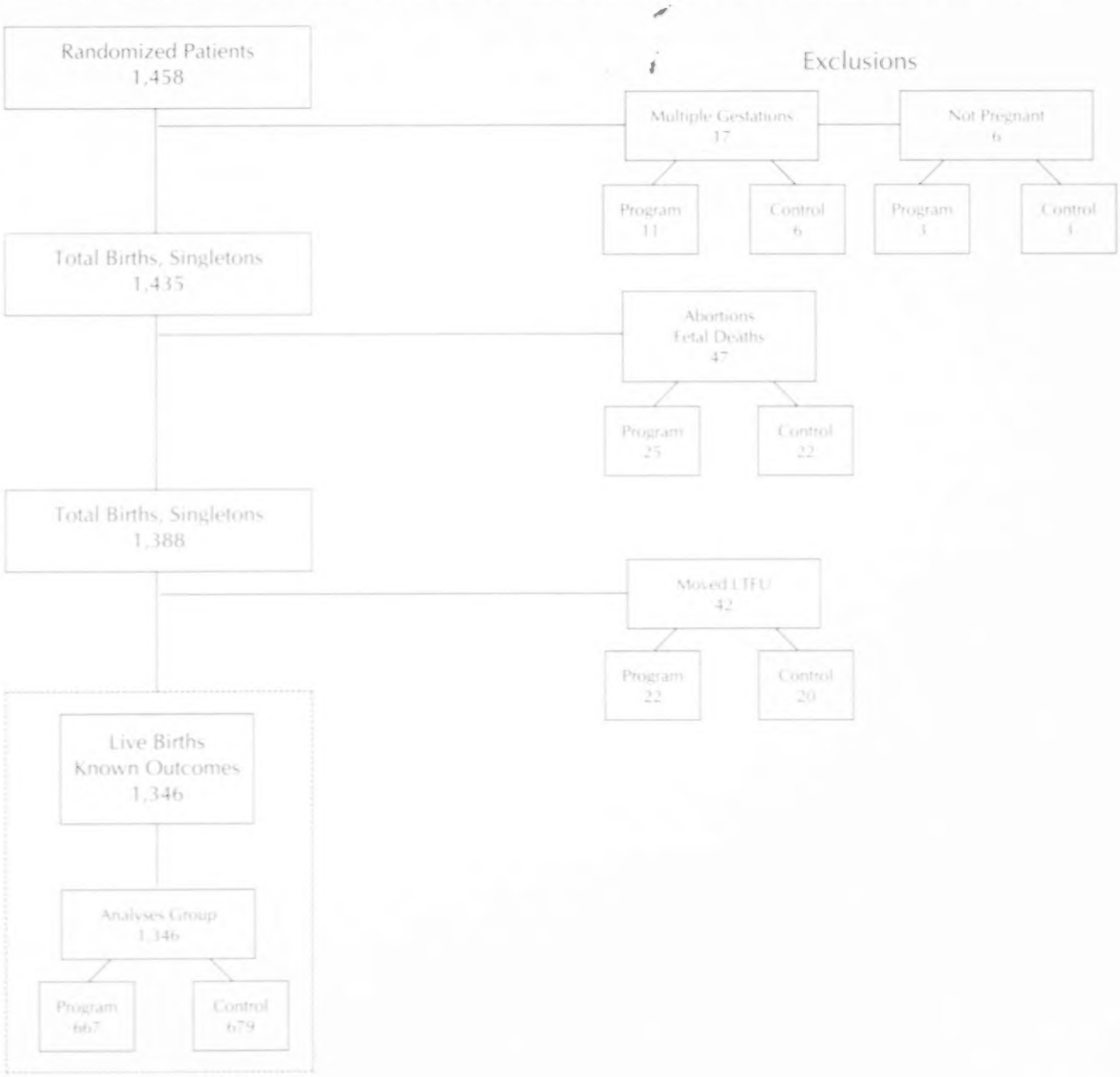

Table 8.1
Selected Maternal Characteristics
South Carolina Randomized Controlled Trial

Maternal Characteristic*	Patient Analytical Status: Total Singletons Number	Total Singletons Percentage	Excluded Number	Excluded Percentage	Analytical Group Number	Analytical Group Percentage
Total Participants	1,435	100	89	6.6	1,346	93.4
Race						
White	759	52.9	41	46.1	718	53.3
Black	648	45.2	34	38.2	714	45.6
Other	6	0.4	0	0.0	6	0.4
Missing	22	1.5	14	15.7	8	0.6
Education (Years)						
12+	110	7.7	7	7.9	103	7.7
12	392	27.3	19	21.3	373	27.7
<12	887	61.8	47	52.8	840	62.4
Missing	46	3.2	16	18.0	30	2.2
Marital Status						
Married	633	44.1	33	37.1	600	44.6
Single	772	53.8	34	38.2	738	54.8
Missing	30	2.1	22	24.7	8	0.6
Age (years)						
Under 18	249	17.4	4	4.5	245	18.2
18–34	1,069	74.5	32	35.9	1,037	77.1
Over 34	43	3.0	1	1.1	42	3.1
Missing	74	5.2	52	58.4	22	1.6
Risk Score						
0–9	126	8.8	8	9.0	118	8.8
10–19	1,056	73.6	58	65.2	998	74.1
20–29	176	12.3	9	10.1	167	12.4
30+	43	3.0	3	3.4	40	3.0
Missing	34	2.4	11	12.4	23	1.7
Gravida						
1	264	18.4	7	7.9	257	19.1
2–4	915	63.8	56	62.9	859	63.8
5+	231	16.1	13	14.6	218	16.2
Missing	25	1.7	13	14.6	12	0.9

* *No statistically significant difference occurred between program and control for any of the parameters above.*

Table 8.2
Selected Maternal Characteristics
South Carolina Randomized Clinical Trial

Maternal Characteristic	Patient Type: Program (P) Number	Program (P) Percentage	Control (C) Number	Control (C) Percentage
Total Participants	667		679	
Race				
White	310	46.5	304	44.8
Black	348	52.2	370	54.5
Other	5	0.7	1	0.1
Missing	4	0.6	4	.6
Education (years)				
12+	55	8.2	48	7.1
12	183	27.4	190	28.0
<12	421	63.1	419	61.7
Missing	8	1.2	22	3.2
Marital Status				
Married	300	45.0	300	44.4
Single	364	54.6	374	55.1
Missing	3	0.4	5	0.7
Age (years)				
Under 17	127	19.0	118	17.4
18–19	85	12.7	114	16.8
20–34	427	64.0	411	60.5
35+	17	2.5	25	3.7
Missing	11	1.6	11	1.6
Risk Score				
0–9	61	9.1	51	7.5
10–19	490	73.5	508	74.8
20–29	85	12.7	82	12.1
30+	18	2.7	22	3.2
Missing	13	1.9	10	1.5
Gravida				
1	134	20.1	123	18.1
2–4	411	61.6	448	66.0
5+	117	17.5	101	16.0
Missing	5	0.7	7	1.0

Table 8.3
South Carolina Randomized Controlled Trial
Service Statistics (Live Births), Analytical Group

Year of Recruitment	Total		Program		Control	
	Number	Percentage	Number	Percentage	Number	Percentage
	1,435	100.0	667	100.0	679	100.0
1983	125	9.3	62	8.9	63	8.8
1984	405	30.1	194	28.0	211	31.0
1985	420	31.2	207	30.5	213	30.8
1986	371	27.6	191	28.0	180	26.3
Missing	25	1.8	12	4.3	11	3.3
Gestational Age at Randomization (Onset of Care)						
<12	81	6.0	29	4.3	52	7.7
12–16	247	18.4	114	17.1	133	19.6
17–20	252	18.7	132	19.8	120	17.7
21–24	251	18.6	128	19.2	123	18.1
25–29	313	23.3	188	28.2	125	18.4
>30	124	9.2	63	9.4	61	9.0
Missing	78	5.8	13	1.9	65	9.6
Clinic Site						
GHS*	180	13.4	95	14.2	85	12.5
MRMC†	233	17.3	109	16.3	124	18.3
MUSC‡	487	36.2	242	36.3	245	36.1
RMH§	190	14.1	93	13.9	97	14.3
SGH¶	255	18.9	127	19.0	128	18.9
Missing	1	0.1	1	0.3	—	0.0

*Greenville Hospital System
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‡Medical University of South Carolina
§Richland Memorial Hospital
¶Spartanburg General Hospital

Table 8.4
Birthweight Outcomes
South Carolina Randomized Clinical Trial (Live Births)

Birthweight Group	Patient Type: Program (P) Number	Program (P) Percentage	Control (C) Number	Control (C) Percentage	Odd Ratio (95% CL) C vs. P
Total					
VLBW	24	3.6	28	4.1	1.15 (0.7–2.0)
LBW	103	15.4	111	16.3	1.09 (0.8–1.4)
NBW	540	81.0	540	79.6	
Total	667	(100.0)	679	(100.0)	

Table 8.5*
Birthweight Outcomes
South Carolina Randomized Clinical Trial (Live Births)

Birthweight Group	Patient Type: Program (P) Number	Program (P) Percentage	Control (C) Number	Control (C) Percentage	Odd Ratio (95% CL) C vs. P
White					
VLBW	11	3.5	8	2.6	0.73 (0.3–1.9)
LBW	38	12.3	33	10.8	0.83 (0.5–1.3)
NBW	261	84.2	263	86.5	
Total	310	100.0	304	100.0	
Black					
VLBW	12	3.4	20	5.4	1.6 (0.8–3.3)
LBW	64	18.4	76	20.5	1.25 (0.9–1.8)
NBW	272	78.2	274	74.1	
Total	348	100.0	370	100.0	
Risk Group 10–19					
White					
VLBW	6	2.4	5	2.0	0.83 (0.2–2.7)
LBW	27	10.8	24	9.6	0.86 (0.5–1.5)
NBW	216	86.7	221	88.4	
Total	249	100.0	250	100.0	
Black					
VLBW	6	2.6	17	6.7	2.85 (1.1–7.3)
LBW	40	17.0	46	18.0	1.35 (0.9–2.1)
NBW	189	80.2	192	75.3	
Total	235	100.0	255	100.0	

* *Table 8.5 includes only white and black infants.*

A Prematurity Prevention Project in Northwest North Carolina

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Introduction

Premature or low birthweight (LBW) births are a major cause of infant mortality and neonatal and postneonatal morbidity.[1,2] Rates of LBW and very low birthweight (VLBW) births are high in southern states of the United States and have not shown great improvement over the past decade.[3] An example of this lack of improvement is shown in the rates of LBW and VLBW births in northwest North Carolina from 1980 to 1985 (see figure 9.1).

Although the basic mechanism or cause of most premature births is not known, prevention strategies may be of some use. Papiernik[4] and Creasy[5] have described their experiences

with a system of risk assessment, patient education, intensive prenatal care, increased maternal rest, appropriate use of tocolytic drugs, and other methods which were successful in improving birth outcomes. Papiernik[4] reported success with this program in a number of different populations in metropolitan France and Martinique; Creasy[5] reported success in patients of a clinic in San Francisco. Recently, however, these encouraging reports have been tempered by results from randomized prospective trials of this risk assessment-educational model. Main[6] reported a lack of effectiveness in a small group of patients in Philadelphia, and early reports of the multicenter March of Dimes trial have not indicated effectiveness in the patients studied.*

The purpose of this chapter is to report on our experience with a LBW or prematurity prevention project in northwest North Carolina.

Methods

This project was implemented in the 20-county area in northwest North Carolina constituting Perinatal Care Region 2. This region is a mixture of urban and rural counties with approximately 21,000 births per year, approximately one-fourth of North Carolina's total number of births per year. The program was based on the principles of Creasy and included the following: Risk assessment and education for all patients, routine vaginal examination at 26 weeks' gestation to evaluate cervical change, more intensive prenatal care for patients thought to be at risk, and hospital care including tocolytic drugs when appropriate. The program was presented to private obstetricians and family physicians and to county health department clinics throughout the region. Details of the development and presentation of the program have been described elsewhere.[7,8]

All health department clinics in the region chose to participate in the project. A portion of the private physicians chose to participate, and the remainder of the private providers chose not to participate in the program. Since patients of public health department clinics are low-income patients known to be a high-risk group, the results from these patients were excluded from the present evaluation and comparisons were made between births of patients of providers who participated in the program and births of patients whose physicians chose not to participate. Using birth data obtained from the North Carolina State Center for Health Statistics, birth outcomes were examined for residents of Perinatal Region 2 for 1985 and 1986, the first two years of full project implementation. Births of less than 500 g were excluded from the results, as were births to women who did not receive prenatal care. Comparisons were then made between birth results of private patients enrolled in the program and private patients not enrolled in the program.

Results

In 1985 and 1986, 12,704 births occurred to private patients enrolled in the program and 23,757 births occurred to women whose physicians chose not to enroll patients in the program. The results are shown, categorized by

* *Morton, R. Personal communication.*

race, in table 9.1 and figures 9.2–9.5. Births listed as "nonwhite" are almost entirely of black race, as very few other nonwhite births occur in this region. These results are shown as the percentage of births less than 1500 g (VLBW), less than 2500 g (LBW), less than 38 weeks' (266 days) gestation, and less than 38 weeks' gestation and less than 2500 g (premature low birthweight [P-LBW] births).

The percentage of births less than 2500 g was significantly lower for both white and nonwhite patients enrolled in the project compared with patients not enrolled in the project. The percentage of births less than 1500 g was lower in patients enrolled in the project, but this difference did not reach statistical significance in nonwhite patients, as the absolute number of births was small. Premature births (less than 38 weeks' gestation) were less frequent in nonwhite patients enrolled in the project. No significant difference was observed for rates of premature births in white patients or for rates of P-LBW births in white or nonwhite patients.

Discussion

Clear differences exist in birth results of private patients enrolled in the program compared with those not enrolled. As all public patients in Region 2 were enrolled in the program, no similar comparison group exists. Evaluation of results in the public patients by other methods is under study.

The results of this study may be biased by differences in the characteristics of patients participating in the project compared with those not participating in the project. Although a greater proportion of the nonproject births were nonwhite or black, differences in birth outcomes remained when these results were examined by race. An earlier evaluation of LBW births in Perinatal Care Region 2, conducted in 1985 by Buescher,[9] used a multivariate analysis. After correction for a number of risk factors, including age, race, education, and marital status, the relative odds ratio for LBW birth to women not enrolled in the project was 1.32 higher than for women enrolled in the project.

Although better birth outcomes occurred to nonwhite or black women enrolled in the project, the rates of premature or LBW births remained roughly twice as high for nonwhite births as for white births. This disparity was seen both in project and nonproject births.

The difference in the apparent success of this prevention model in this project (and in the reports of Papiernik and Creasy) compared with the reports of Main and the March of Dimes trial may be related to characteristics of the populations involved. We have previously reported that LBW births in patients of a public health department clinic are frequently related to premature rupture of the fetal membranes, impaired fetal growth, or medical problems.[10] Prevention strategies are unlikely to affect the outcome in pregnancies with these problems. In contrast, in our previous study, private patient LBW births were more likely to be related to idiopathic premature labor, which may be favorably influenced by prevention techniques. Thus, the relative success or effectiveness of the Papiernik-Creasy prevention model may depend in part on the characteristics of the population for whom it is employed.

Although a difference was seen in the rates of LBW births between women enrolled in the project and those not enrolled, no difference was seen in the rates of P-LBW births. Kessel et al. have previously found that national trends in P-LBW birth rates may be more resistant to improvement than those of term LBW birth rates.[11]

The apparent improvement in the rates of VLBW births to patients enrolled in this project is encouraging. These births are the most likely to have adverse outcomes,[1,2] and even modest reductions in the rates of VLBW births can have significant social and financial impact.[8]

In summary, the results of this project indicate that this prematurity prevention model can be utilized in private patients in a southern state. Improvement in LBW rates occurred in both white and black patients of private providers who utilized the program.

ACKNOWLEDGMENT

The authors are indebted to Michael Patetta of the North Carolina Center for Health Statistics for his assistance in collecting pertinent data from birth certificate information.

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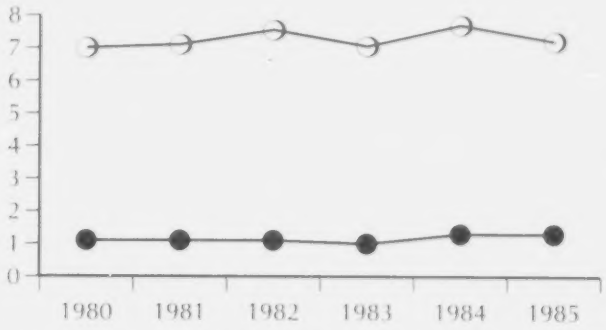
Statistical Findings: A Prematurity Prevention Project in Northwest North Carolina

Table 9.1
Private Births in Northwest North Carolina
1985–86

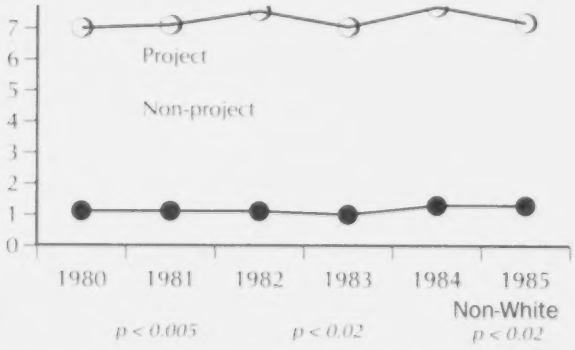
	Project	Non-Project	X^2	*P*
Total Births	12,704	23,715		
Percentage Breakdown:				
< 1500 g	0.75	1.33	25.19	< 0.005
< 2500 g	5.94	7.32	25.06	< 0.005
< 38 wks	9.54	10.71	12.09	< 0.005
P-LBW	3.83	4.11	1.67	NS
White Births	11,035	19,051		
	Project	Non-Project		
Total Births	12,704	23,715	X^2	*P*
Percentage Breakdown:				
< 1500 g	0.60	1.04	15.95	< 0.005
< 2500 g	5.35	6.05	6.34	< 0.02
< 38 wks	8.62	8.87	0.55	NS
P-LBW	3.41	3.52	0.26	NS
Non-White Births	1,669	4,664		
	Project	Non-Project		
Total Births	12,704	23,715	X^2	*P*
Percentage Breakdown:				
< 1500 g	1.74	2.25	1.57	NS
< 2500 g	9.83	12.09	6.21	< 0.02
< 38 wks	15.58	18.55	8.07	< 0.005
P-LBW	6.58	6.56	0.00	NS

Figure 9.1
Rates of LBW and VLBW Births in Northwest North Carolina*



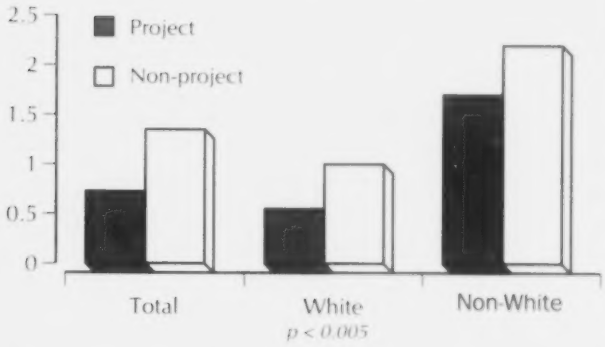
** Percentage rates of LBW (500–2500 g) births in northwest North Carolina are shown in the upper scale of the chart and rates of VLBW (500–1500 g) births are shown in the lower scale.*

Figure 9.2
Rates of LBW Births Within the Project vs. Rates Among Unenrolled Private Patients*



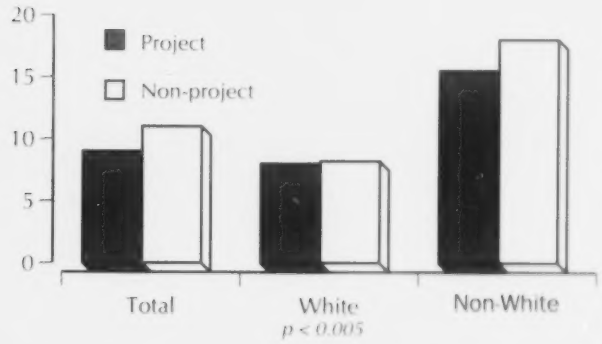
** Percentage rates of LBW (500–2500 g) births in private patients enrolled in the project (gray bars) are compared with rates of LBW births in private patients not enrolled in the project (white bars).*

Figure 9.3
Rates of VLBW Births Within the Project vs. Rates Among Unenrolled Private Patients*



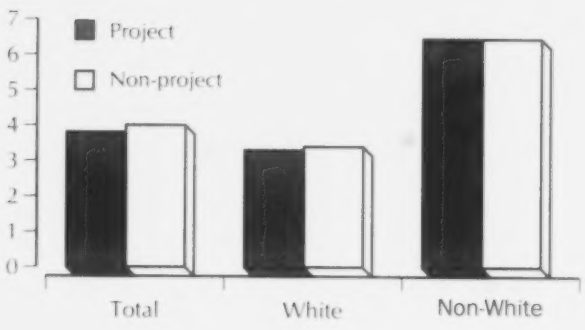
** Percentage rates of VLBW (500–1500 g) births in private patients enrolled in the project (gray bars) are compared with rates of VLBW births in private patients not enrolled in the project (white bars).*

Figure 9.4
Rates of Premature Births (< 38 Weeks' Gestation) Within the Project vs. Rates Among Unenrolled Private Patients*



** Percentage rates of premature births (< 38 weeks' gestation) in private patients enrolled in the project (gray bars) are compared with rates of premature births in private patients not enrolled in the project (white bars).*

Figure 9.5
Rates of P-LBW Births Within the Project vs. Rates Among Unenrolled Private Patients*



** Rates of premature low birthweight (P-LBW) births in private patients enrolled in the project (gray bars) are compared with rates in private patients not enrolled in the project (white bars).*

The Family Workers Project: Evaluation of a Randomized Controlled Trial of a Pregnancy Social Support Service

BRENDA SPENCER, PH.D.

INTRODUCTION

The *Short Report,* published in 1980 by the House of Commons Social Services Committee[1] highlighted widespread variations in perinatal health among different areas of the country. Birthweight is acknowledged to be one of the best available indicators of perinatal health,[2] and, using this indicator, the Manchester region compared badly with the country at large. Here, 10.2 percent of all newborn infants weighed less than 2500 g, compared with a figure of 7.3 percent for England and Wales as a whole.[3]

Low birthweight arises as a consequence of premature onset of labor or retarded fetal growth, and is more commonly found among socially disadvantaged women.[4] Psychosocial

stress is one possible mechanism by which social disadvantage may give rise to poor pregnancy outcome.[5–7] Factors often cited as contributing to psychosocial stress are low income, inadequate access to and consumption of services, inadequate access to information, lack of physical effort, isolation, improper diet, poor living conditions, ambivalence about the pregnancy, and lack of social support.[8–14]

While it is not possible for health services to reverse the social disadvantage reflected in perinatal statistics, it may be possible to compensate for it by the appropriate redirection of provision. This possibility prompted the institution of the South Manchester Family Worker Scheme, which aimed to provide additional social support for women at above-average risk of giving birth to a low birthweight baby. It was intended that this support would reduce the level of stress, thereby improving the well-being of the mothers-to-be and, ultimately, the health of their babies.

The role of the family worker is modeled after that of the *travailleuse familiale* who had been provided as part of the Maternal and Child Health Service in the Département of Seine-Saint-Denis.[15] In Manchester, short-term funding for family workers was obtained from the Manpower Services Commission. Women selected for the posts were hired on the basis of personality and general life experience; they had no formal qualifications in health or social services. The service adopted a client-centered approach, with the tasks of the worker varying according to each client's situation. In practice, these ranged from providing help with obtaining state benefits, housing, shopping and other domestic work, and childcare, to promoting appropriate use of health and social services, and community facilities; and generally acting as confidante.[16]

The effect of intervention by the family workers was evaluated in the form of a randomized controlled trial. The trial was designed to evaluate the potential impact of such a service; therefore, randomization took place before knowing which women would eventually accept a family worker. The "treatment" did not consist of having the assistance of a family worker, but in receiving the offer of a family worker.

Method

The trial took place in two phases, from June 1982 to June 1983 and from June 1984 to September 1985. The year-long gap between the two phases was attributable to problems with funding for the family workers. An overview of recruitment and participation in the trial is shown in figure 1. Women eligible for the trial were identified following their registering visit to either of the two maternity units within the South Manchester Health District. Eligibility was determined according to criteria indicating increased risk of giving birth to a low birthweight baby, and was mainly based on national birthweight statistics[4] and on previous research.[17–19] Any woman satisfying at least two of the entry criteria illustrated by an asterisk in table 10.1 was included.

In the second phase of the trial the entry criteria were modified slightly to increase the rate of recruitment. Two new criteria were introduced: "Interpregnancy interval ≤ 6

months" and "parity ≥ 3." Existing criteria were in some cases broadened; for example, what was formerly "previous perinatal death" was extended to "previous fetal/infant death > 12 weeks' gestation and up to 1 year of life", and "marital status single" was extended to include known cohabitees. Also, owing to the problems in using the Registrar General's *Classification of Occupations*[1] to classify women's occupations by social class, the decision was made to categorize certain occupations for women as belonging to social classes IV or V, although they are not officially classified as such (see table 10.1).

As the family worker was intended to play a preventive role, any women registering later than the 20th week of pregnancy were excluded. Intervention began as soon after registering as could practically be arranged. Asian women were excluded from the trial in view of the lower birthweight distribution of these ethnic groups.[2] Entry to the trial was also confined to those living within the district and predefined adjoining areas. During the two periods of recruitment the notes of all women attending the registering clinics were screened. In an average month of recruitment those eligible for the trial represented approximately one-quarter of all women registering at the 2 clinics, giving a final total of 1,288 women. Allowing for women lost to follow-up and pregnancy loss, it was estimated that each group would have approximately 600 cases; this would give a 76 percent chance of detecting a difference in mean birthweight of 77 g between the two groups, significant at the 5 percent level (two-tailed test) assuming a standard deviation of 500 g. (It was estimated that, if the intervention was to be clinically of interest, a difference in mean birthweight of 77 grams between the groups would need to be detected. This figure is derived from the difference in mean birthweight between social classes I and II combined and III, IV, and V combined); however, the chance of detecting a decrease in the proportion of low birthweight babies from 10.2 percent to 7.3 percent, significant at the 5 percent level, would be less than 50 percent.

Following recruitment, participants were randomly allocated to either the control or the experimental group using random number tables. The women in the experimental group were then sent information describing the scheme, as illustrated in figure 10.2, and a letter indicating a date and approximate time when the family worker supervisor would call. On her visit, the supervisor explained the scheme in more detail, ascertained whether the woman was interested in having a family worker and, if so, which of the workers would be most appropriate. In the first phase, the scheme consisted of 10 full-time workers, plus a supervisor and project assistant; in the second, the equivalent of 20 full-time workers were employed on a full- and part-time basis, plus a supervisor, assistant supervisor, and project assistant (although during the last 3 months the staffing was reduced to one-third). On average, a full-time worker would have six clients, each of whom would receive one to two visits per week (although, as the service was flexible to the needs of each individual, some received more extensive help than this and others received less). Information on birthweight, together with other outcome data on perinatal health, was collected from the

women's hospital records. Results have been analysed (t and X^2 tests) using the SPSS computer package.[22]

Results

The population covered by the study is shown in table 10.1. As illustrated, the process of randomization was effective in ensuring comparability between the two groups. A minimum of two criteria were sufficient to qualify for entry to the study, but approximately two-thirds of those recruited satisfied three or more criteria.

Of the women in the intervention group who were eligible to have a family worker, 41.4 percent received help. As shown in table 10.2, there were a number of reasons why the remainder of the experimental group could not, or did not, accept the offer of a family worker, the most common being because enough support was already available.

Of the 1,288 women recruited to the trial (see figure 10.1), outcome data were unavailable for 52 women (25 in the control and 27 in the experimental group), the most common reason being relocating out of the area before childbirth (see table 10.3). The characteristics of women for whom no outcome was obtained did not differ from those on whom the final analysis was conducted. In addition, twins were excluded from the outcome analysis, which was therefore conducted on 1,227 women.

Data on mean birthweight and gestation for livebirths and stillbirths are presented in table 10.4. No statistically significant differences were found between the two groups. The experimental group contained a slightly higher proportion (53.1%) of male babies than did the control group (47.7%). Therefore, in view of the fact that male babies are on average heavier than female babies, male and female birthweights are presented separately in the tables and figures. Table 10.5 presents outcome in terms of the proportion of babies in each group who were of low birthweight, the proportion who were assessed as small for gestational age, and the proportion who were born before term. Figures are also included on very preterm and very low birthweight births. Being small for gestational age was defined as those babies whose birthweight fell below the 10th centile on the birthweight gestation charts for males and females published by Milner and Richards.[23] The odds ratios calculated on the proportions and the associated confidence intervals demonstrate the similarity of results obtained from the two groups.

The outcome of all pregnancies in terms of survival is shown in table 10.6. The proportions of pregnancies resulting in a livebirth in the control and experimental groups were 96.5 percent and 95.4 percent, respectively (stillbirth was defined as any baby born dead at or after 28 weeks' gestation). Of the livebirths, three babies in the control group and one baby in the experimental group died within the first week, the latter death being due to a lethal congenital malformation. The largest discrepancy in the table is in the number of terminations carried out for social reasons; however, examination of the relationship between the stage in the pregnancy at which these terminations took place and the timing of the visit of the family worker supervisor did not suggest any connection between the two.

Details on gestational age for all pregnan-

cies, excluding those terminated by induced abortion, are presented in table 10.7. There was no evidence to suggest any differences in distribution of gestational length observed in the two groups. (In order to obtain the best estimate of gestational age, the woman's dates were used if she was certain of the date of her last menstrual period. For those who were uncertain, gestational age was based on assessment by ultrasound scan if this was performed before the 20th week of pregnancy or, where no such reading was available, was taken from the woman's uncertain dates. A comparable proportion of women in the control and experimental group were able to report their dates with certainty.)

As two maternity units were involved in the study, their entry and outcome data were studied separately to check for any possible discrepancies between the two hospitals. It was found that approximately equal numbers of trial participants had been recruited from each center, and the profile of the two populations was equivalent both in terms of characteristics at entry to the trial and mean birthweight and length of gestation of the baby.

Discussion

From the results it is clear that making available the provision of a family worker service to the at-risk group as defined did not significantly influence either the overall mean birthweight or the proportion of low birthweight; nor was there any indication that either of the component elements of low birthweight, that is, preterm birth and fetal growth retardation, were affected.

As with many clinical trials, the size of the study population is perhaps not sufficient for any definite conclusions to be drawn, the final numbers and standard deviation (550 g) providing a 69 percent power of detecting the difference in birthweight felt to be clinically important. There was, however, no indication in the results of an outcome favoring the experimental group, and, indeed, the actual mean birthweight of the control group was greater than that of the experimental group. Moreover, the 95 percent confidence interval for the difference between the mean birthweights does not include a difference of 77 g in favor of the experimental group. In addition to birthweight and gestation, a number of other outcome measures were examined with no suggestion of any clinically important differences between the two groups.

There are a number of possible ways in which these results might be interpreted, each interpretation having different implications in terms of policy and future research. The first conclusion which may be drawn is that the social support of a family worker given to a woman in pregnancy does not influence the likelihood of her giving birth to a low birthweight baby. The hypothesis that social support could improve perinatal outcome, as measured by birthweight, was developed on the basis of a substantial amount of previous research. It has variously been suggested that stress and lack of social support give rise to adverse outcome and that intervention programs may mitigate their effect.[24,25] Our experience in conducting the scheme strongly indicated that family workers increased the subjective well-being of their clients. Nonetheless, it could be that the increase in well-being had no impact

on the development of the fetus, or that it was insufficient to effect any change. Perhaps for those women at greatest risk the support of a family worker was not able to counterbalance the adverse factors leading to low birthweight; or their help was not intensive enough; or, beginning after the first trimester, it came at too late a stage in the process.

Another line of interpretation concerns the target group on whom the study was conducted. It might be argued that the criteria applied resulted in the selection of a group which was inappropriate for the intervention. The group may be said to be inappropriate either because just over one-half of those offered a family worker did not or were not able to accept, or because the entry criteria did not adequately target those most likely to benefit from additional support.

Women eligible for the trial were not prescreened to select those who would be more likely to accept a family worker. Although a certain level of nonacceptance was expected, since not all women would need additional support, the nonacceptance rate obtained in practice (58.7%) was nonetheless higher than was felt desirable and would obviously partially account for the nonsignificant findings. Analyses were therefore conducted between those women who did accept and those who did not accept combined with the control group. These did not show any statistically significant differences between the two groups, although, owing to the uneven groupings, the chance of detecting a difference was unacceptably low at 52 percent, and, in addition, the groups were not comparable because some criteria were associated with a higher rate of acceptance than were others. There tended to be a greater acceptance of the service among women who were eligible because they had experience of previous adverse pregnancy outcome, or who qualified under the "social class IV or V/unemployment" criterion. An analysis of variance to examine the effect of these criteria on eventual birthweight outcome showed that the weight of babies born to women who entered the trial on the grounds of previous adverse pregnancy outcome was significantly lower than that of others born in the trial ($p < .001$).

The criteria used resulted in the selection of a population with a rate of low birthweight (live-births) of 8.6 percent The overall rate for South Manchester during the years the trial took place was only marginally lower than this figure.[29,30] (Earlier published figures based on the Manchester area as a whole[1] are higher because the Central and North Districts have higher rates.) Given that trial participants were identified as being at above-average risk, one might have anticipated a higher rate of low birthweight relative to the local population than was obtained. It may be that the exclusion of Asian women from the trial accounted in part for this discrepancy, but, even taking this factor into account, it does appear that the criteria did not prove sufficiently stringent to identify those most at risk. Indeed, since during the second phase they applied to approximately one-quarter of all those registering, they might be considered extensive.

Although psychosocial stress may give rise to the birth of a low birthweight infant, not all low birthweight is attributable to this cause. Similarly, the risk factors adopted as criteria reflect both collectively and individually a combination of social and medical risk, not all of which could potentially be reduced by social

support. The choice of low birthweight risk factors as criteria directs the intervention to a group with a potentially higher rate of low birthweight; however, this may nonetheless result in an inadequate targetting of those most likely to benefit from the intervention, since only a certain proportion of that risk could be mitigated through social support. It may therefore be argued that only certain groups within the overall at-risk population stand to benefit from additional social support. Particular concern is often expressed about the needs of adolescent mothers, for example. A subgroup analysis of women less than 20 years old expecting their first child showed a smaller proportion of low birthweight and premature babies in the experimental group, but because of small numbers the results were statistically inconclusive.

The adoption of low birthweight and preterm delivery as general indicators of perinatal health is standard, but these are nonetheless proxy measures and may not be entirely appropriate for a trial of this kind. Very low birthweight is more strongly associated with adverse outcome, but, since it is a much rarer event, its use as a measure would require larger trials than it is usually feasible to mount. The overview of research on social support during pregnancy by Elbourne and Oakley (see pages 203–224) reports that, in common with the Manchester study, the two other trials in which social support has been the primary intervention found a non-statistically significant fall in the rate of very low birthweight infants. Even after combining results with such small numbers, however, no conclusions can be drawn.

The trial was designed to be population based and, broadly speaking, to be conducted under conditions similar to those which prevail under nonexperimental conditions. For this reason, entry criteria were based on routinely available data from medical records, and no additional prescreening took place. This approach is similar in concept to that of the pragmatic trial as described by Schwartz et al.[30] Given the findings of the trial, however, it is apparent that simply providing a service and targetting it on one-quarter of the population defined as at above-average risk according to a mixture of broadly based criteria, will not affect the incidence of low birthweight in that population. On the basis of our experience with the South Manchester Family Worker Scheme, we would therefore advocate that future research be conducted to ascertain whether social support through family workers may be effective for certain groups within the overall at-risk population. This would entail closer targetting of those most likely to benefit using only criteria indicative of stress, social isolation, or deprivation, and including in the trial only those women both prepared and able to accept the help of a worker. We would also recommend that future research include outcome variables which assess maternal well-being in addition to clinical indicators of the baby's health.

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Statistical Findings: The Family Workers Project: Evaluation of a Randomized Controlled Trial of a Pregnancy Social Support Service

Figure 10.1
Overview of Trial

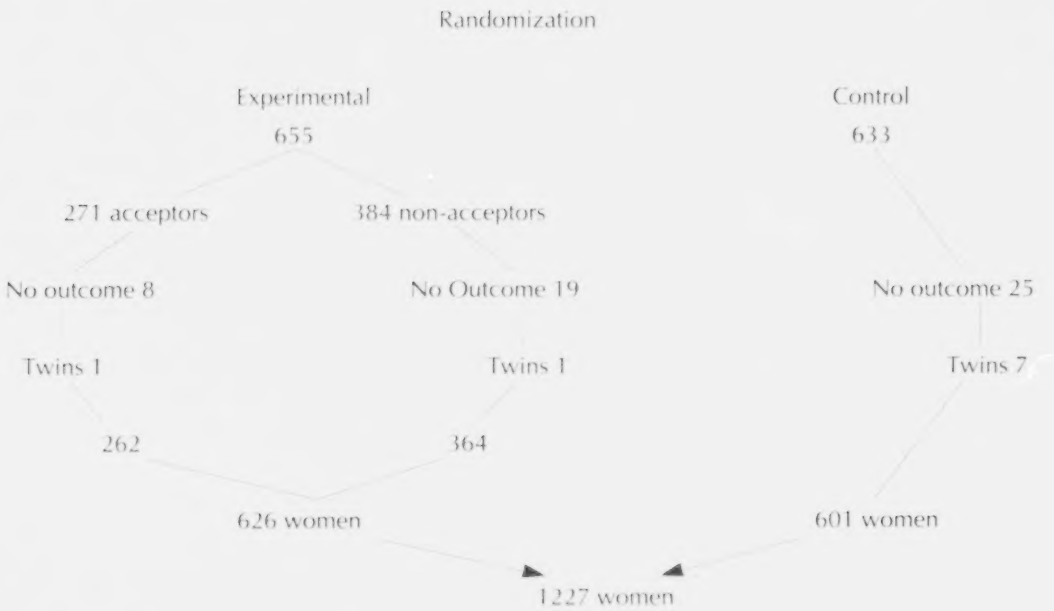

Table 10.1
Study Population

		Experimental N = 655		Control N = 633	
		Mean	Standard deviation	Mean	Standard deviation
Age (mean, standard deviation)*		23.0	5.2	23.2	5.4
Percentage less than 20 years		45.5		43.6	
Weight (kg)		57.2	10.1 (12)*	57.4	11.2 (7)*
Height (m)		1.6	0.7 (20)*	1.6	0.7 (13)*
$\frac{\text{Weight}}{\text{Height}^2}$		22.3	3.6 (30)*	22.6	4.0 (20)*
		Number	Percentage	Number	Percentage
Underweight*		247	37	222	35
Parity %	0	415	63	398	63
	1–2	165	25	163	26
	3+	75	12	72	11
Previous low birthweight (< 2500 g)	0	587	90	574	91
	1	61	9	52	8
	>1	8	1	8	1
Previous preterm birth (< 37 weeks)	0	605	92	578	91
	1	42	6	47	7
	>1	8	1	8	1
Previous spontaneous abortion 12–28 weeks	0	634	97	610	96
	1	15	2	22	4
	>1	6	1	1	1
Previous perinatal death 28 weeks–1st week of life	0	641	98	614	97
	1	14	2	19	3
	>1	—	—	—	—
Previous neonatal and post-natal deaths 2nd week–51st week life	0	640	98	620	98
	1	15	2	12	2
	>1	—	—	1	1
Previous terminations for medical reasons	0	646	99	619	98
	1	9	1	14	2
	>1	—	—	—	—

* *Number of cases for which information was unavailable*

Table 10.1 (Continued)
Study Population

		Experimental		Control	
		Number	Percentage	Number	Percentage
Previous terminations for social reasons	0	590	90	568	90
	1	60	10	59	9
	>1	5	1	6	1
Inter-pregnancy interval < 6 months†		27	5	24	4
Single/widowed/divorced/separated†		398	61	376	59
Woman's social class IV or V or unemployed‡		511	78	477	75
Partner's social class IV or V or unemployed (Percentage of those with partner only)		216	63	219	62
Diabetic		2	1	1	1
Smoking (number of cigarettes per day)	0	326	50	313	49
	1–5	69	11	59	9
	5–20	247	38	243	39
	>20	11	2	14	2

† entry criteria

‡ Women's social class IV or V includes single/widowed/divorced women, nursing auxiliaries, shop/sales assistants and hairdressers, and all unemployed and unclassified women. Women unemployed includes housewives and students.

Partner unemployed includes men in prison, self-employed, students and disabled/sick.

Table 10.2
Reasons for Non-Acceptance

	Number	Percentage
Not in when visited	91	13.9
No longer/never was pregnant	15	2.3
Moving out of study area	39	6.0
Employed full-time	41	6.3
Not interested	55	8.4
Well supported	143	21.8
Total non-acceptors	384	58.7
Acceptors	271	41.3
Total	655	100.0

Table 10.3
Outcome Information Not Obtained

	Experimental		Control	
Reason Outcome Information Not Obtained	Number	Percentage	Number	Percentage
Moved	11	1.7	13	2.0
Transferred to hospital outside study area	5	0.8	3	0.5
No trace	3	0.5	3	0.5
Medical record unavailable	1	0.1	0	0.0
Not pregnant	7	1.1	3	0.5
Home delivery	0	0.0	3	0.5
Total	27	4.2	25	4.0

Table 10.4
Mean Birthweight (Singleton Live and Stillbirths) And Length of Gestation

	Experimental			Control					95% Confidence Interval on difference between means
	Number	Mean	Standard deviation	Number	Mean	Standard deviation	Mean difference	*p*	
Birthweight: All	602 *	3179.6	549.9	581	3214.5	553.5	-34.9	0.3	-97.8 to 28.0
Female	282	3113.3	511.9	304	3146.3	522.4	-33.0	0.4	-90.5 to 24.5
Male	320	3238.0	575.8	277	3289.3	577.5	-51.3	0.3	-143.8 to 41.2
Gestational age (days)	603	279.0	18.7	581	278.4	19.1	0.6	0.6	-1.6 to 2.8

* *Birthweight missing for one stillbirth*

Table 10.5
Proportion of Low Birthweight, Small for Gestational Age, and Preterm Babies

	Experimental Number	Experimental Percentage	Control Number	Control Percentage	Odds ratio	95% Confidence Interval on odds ratio
Number of low birthweight babies (<2500 g) live births and stillbirths	54*	8.8	50	8.6	1.0	0.7 to 1.6
livebirths only	52	8.7	49	8.4	1.0	0.7 to 1.6
Number of very low birthweight babies (<1500 g)	5	0.8	6	1.0	0.8	0.3 to 2.5
Number of small for gestational age**	61	10.0	59	10.2	1.0	0.7 to 1.5
Number of preterm babies (<37 weeks)**	60	10.0	54	9.3	1.1	0.7 to 1.6
Number of very preterm babies (<33 weeks)**	9	1.5	11	1.9	0.8	0.3 to 1.9

* *Birthweight missing for one stillbirth* ** *Live and stillbirths*

Table 10.6
Outcome of Pregnancy

Outcome of pregnancy	Experimental N = 626		Control N = 601	
	N	%	N	%
Termination for medical reasons	3	0.5	1	0.2
Termination for social reasons	11	1.8	1	0.2
Miscarriage: <12 weeks	3	0.5	6	1.0
≥12 weeks	6	1.0	11	1.8
gestation not known	0	0.0	1	0.2
Stillbirth: antepartum	5	0.8	0	0.0
intrapartum	0	0.0	0	0.0
gestation not known	1	0.2	1	0.2
Live birth	597	95.4	580	96.5
Early neonatal death (1-7 days)	1*	0.2	3**	0.5
Late neonatal death (8-28 days)	0	0.0	0	0.0
Survivors at 1 month	596	99.8	577	99.5

* *Due to lethal congenital malformation*
** *None due to lethal congenital malformation*

Table 10.7
Categorization of Gestational Age, Excluding Terminations for Both Social and Medical Reasons

Number of Weeks' Gestation	Experimental N = 626		Control N = 601	
	N	%	N	%
0-24 (<174 days)	9	1.5	20*	3.3
25-27 (175-195 days)	2	0.3	1	0.2
28-31 (196-223 days)	5	0.8	7	1.2
32-36 (224-258 days)	53	8.7	44	7.4
37-41 (259-293 days)	456	74.5	443	73.9
42+ (>294 days)	87	14.2	84	14.0
Total	612	100.0	599	100.0

* *Gestational age was unavailable for one miscarriage. For this case gestation was assumed to be <174 days.*

The Social Support and Pregnancy Outcome Study

Ann Oakley
Lynda Rajan, M.D.

Introduction

The Social Support and Pregnancy Outcome Study (SSPO) is a randomized controlled trial of a social intervention involving home visits to women at high risk of giving birth to a low birthweight (LBW) baby. It was organized and coordinated from the Thomas Coram Research Unit (TCRU), part of the University of London Institute of Education, and funded by the British Department of Health and Social Security (DHSS) for a period of three years, from September 1985 to August 1988. The trial itself ran from January 1986 to November 1987. This chapter describes the background and methodology of the study and presents some of the initial findings. At the time of writing, data analysis is still in progress.

Background and Aims of the Study

The SSPO study is an attempt to assess the effect of social support in pregnancy on a range of pregnancy outcomes. An important reason for undertaking the study was to investigate the potential effectiveness of social support in preventing adverse clinical outcomes, particularly low birthweight. The study was also designed, however, to evaluate the possible effects of social support on outcomes which are conventionally described as "softer" because they are concerned with the psychosocial health of the mother.[1]

The general background to the study is the concept that health is a social, as well as a medical, product.[2-5] Health is promoted not only by medical services but by a healthy environment which enables individuals to make full use of their own personal and social resources in maintaining health. These resources include the social relationships and networks in which individuals are involved. The health-promoting effect of social support has received increasing emphasis in epidemiological and medical sociological research over the last 20 years. There is now a good deal of evidence that social support promotes health in general.[4-15] There are also both observational and experimental studies demonstrating the relevance of social support to healthy childbearing and childrearing.[6-8] Having reviewed these studies, it seemed important to try to advance the debate concerning the effectiveness of social support in pregnancy by undertaking an intervention study using random allocation to control both those factors known to influence pregnancy outcome and those factors whose effect is yet unknown. Since most previous interventions in this field have provided social support in addition to other services such as health education, psychosocial counseling, or intensified clinical care, an important aim of the SSPO study was to attempt to separate the provision of social support from other types of intervention.

The broad aims of the SSPO study were:

1. To conduct a randomized controlled trial (RCT) of a program of antenatal support and interviewing by midwives in a sample of women at high risk of delivering a LBW infant;
2. To collect information on the social circumstances, health, and self-perceived pregnancy needs of such women; and
3. To evaluate the relevance of data obtained from (1) and (2) to the type of antenatal care currently provided for high-risk women and to the future prevention of LBW and other adverse pregnancy outcomes.

The size of the SSPO sample was initially calculated in relation to the birthweight outcome on the basis of a comparison of mean birthweight between intervention and control groups rather than of the proportion of women in the two groups giving birth to a LBW baby. The latter calculation would have demanded a considerably larger sample size. Using mean birthweight as an outcome required a sample size of 420 to show a significant increase of 150 g in mean birthweight in the intervention group (power of 80%, $p = 0.05$). The actual achieved sample size was 509.

In addition to testing the hypothesis that

a social support intervention in high-risk pregnancy might be capable of increasing mean birthweight, the SSPO study was designed to test the idea that social support might affect the birthweight distribution, some birthweight groups more than others, and particularly those women who were socially unsupported or whose obstetric histories indicated *social* rather than *biological* reasons for previous LBW delivery. Other initial hypotheses were that the provision of additional social support in pregnancy might affect maternal hospital admissions in pregnancy, the incidence of hypertension and other physical morbidities, the length of labor, the use of analgesia, the incidence of instrumental delivery and other such procedures, and, in the postpartum period, the incidence of maternal depression, infant and maternal morbidity and health service use, and the women's confidence as mothers.

Study Design

The study was carried out in four centers, two in the Midlands and two in the south of England. Women registering at these four centers were eligible to enter the trial provided they met the following eligibility criteria: A history of at least one previous low birthweight delivery unassociated with major congenital malformations; booking before 24 weeks' gestation with a singleton pregnancy; and reasonable fluency in English. The first criterion was chosen in order to select an at-risk group so that the chance of showing some effect of the intervention would be maximized. This strategy appears to have been successful, judging from the obstetric and social characteristics of the final study sample, and was considerably easier to carry out than more complex risk scoring systems. Women entering care very late in their pregnancy were excluded from the study in order to allow time for the intervention to be given. Restriction of the study to English speakers was unfortunately necessary, as funding was insufficient to cover the cost of interpreting and translating for non-English-speaking ethnic minority mothers; however, four percent of the final sample identified their ethnicity as Afro-Caribbean, Asian or "mixed," and five percent of the partners were described as belonging to this category.

The social support intervention in the SSPO study was provided by midwives who worked as research midwives on a part-time basis for the duration of the trial, one in each of the four centers. The chief reason for using midwives to provide the intervention was that the Department of Health, which funded the study, was concerned that the interveners employed should, for policy reasons, be representative of a group that already had an established role in maternity services. In the event the study demonstrated benefits of support in pregnancy, the policy implications would then be relatively easier to translate into practice than if staff not linked with the maternity services had acted as sources of support. There is also a sound historical and professional rationale for seeing midwives as potential social supporters, as individual social care for women has always constituted a key element in the professional ideology and practice of midwifery.[9]

Figure 11.1 shows the consent, randomization, and data collection procedures used in the SSPO study. From January 1986 to May 1987, the four research midwives selected from the case notes of all the women registering at the four centers those who fit the study eligibility criteria. The aims and design of the study were then described to each woman. The midwife explained that, if a woman agreed to take part, she would not necessarily receive the social support intervention, but would have a 50/50 chance of being in the control group. The importance of random allocation was emphasized, as was the fact that every woman would receive standard antenatal care, irrespective of study participation or allocation. The midwives also explained that every woman who entered the study would be asked to complete a postal questionnaire six weeks after delivery.

When a woman agreed to take part, the midwife telephoned TCRU for an allocation and then informed the woman to which group she belonged. Women allocated to the intervention group received the social support package in addition to their normal antenatal care; those allocated to the control group had standard antenatal care only. Obstetric data were collected after delivery on all of the women participating in the study.* A postal instrument was used to collect information from the mothers postpartum, both to reduce cost and to avoid the potential problem of the midwives who had provided the social support intervention collecting information they might wish to see establishing the benefits of their work. The two main disadvantages of a postal survey are loss of qualitative material and low response rates. The format of the questionnaire used in the SSPO study encouraged women to write open-ended, unstructured answers if they wished to, and many did; assiduous follow-up of initial nonresponders produced an overall response rate of 95 percent.†

Nature of the Social Support Intervention

The SSPO study was set up to evaluate the potential of nonspecific social support to improve pregnancy outcome. As emphasized above, it was not a study of a health education, intensified clinical care or other directly service-related intervention, but rather an attempt to provide and assess the value of support to women in their own homes during pregnancy in whatever way seemed appropriate to them. The SSPO intervention consisted of a minimum package of three home visits, ideally at 14, 20, and 28 weeks' gestation, plus two telephone calls (or brief home visits for women without telephones) from the research midwives. The midwives were asked to try to provide this minimum package for every intervention group woman and to provide more than this if asked to do so by the woman (providing the midwife's caseload allowed this). In addition, the research midwives were provided with radiopagers, and intervention group women were informed that they could call the midwife assigned to them whenever they wanted to, on a 24-hours-a-day basis.

During the home contacts, the midwives were asked to do a number of things: First of

all, to listen to what women had to say; secondly, to discuss with the women their pregnancy needs and circumstances; thirdly, to give information when required; and lastly, to carry out appropriate referrals to other agencies, such as social workers or hospital specialists. To provide a structure for the interaction between the research midwives and the women they were supporting, three semistructured interview schedules were available, and normally used.[§] A portion of each home contact was tape-recorded to generate a basis for comparing the midwives with one another, and also to provide some qualitative data for the analysis of the study results. After each contact with a woman in her intervention group, the midwife completed a short data sheet on which she assessed the woman's needs, her state of mind, and the type of help given, if any.

Table 11.1 gives some guidance as to how these specifications for the intervention worked in practice. The home visits were carried out at approximately 18, 24, and 30 weeks, somewhat later than planned, due largely to the women registering to hospital and thus being recruited into the trial later than anticipated. Twenty-five percent of the women received less than the minimum social support package (normally because they delivered early) and 70 percent received more than the minimum package. More than one-half of the intervention women were referred by the research midwives to health professionals at some stage in their pregnancies, and one-quarter were referred to welfare agencies; one in five women did not receive referrals of any kind. Information about the specific health topics of smoking, alcohol, and diet was requested and given to 12 percent, 8 percent, and 24 percent, respectively, of the intervention group; one-third of the women were not given any lifestyle information at all. The research midwives were provided with guidelines as to how to respond to specific topics in order to standardize the type of information given. Throughout the trial regular monthly meetings were held in London and attended by all of the midwives. These meetings served a number of purposes, including facilitating the standardization of the social support being given and allowing the research midwives to discuss the inevitably stressful nature of the work involved in giving support to women with large numbers of social and obstetric problems.

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* *Except for two who moved away during the study and could not be traced.*

† *Particular thanks are due to Sandra Stone for this.*

§ *The interview schedules were used partly as a result of experience of the Perth Social Support and Prevention of Preterm Labour Trial, in which it was found that sometimes conversations between research midwives and intervention group women did not easily get off the ground, due to lack of an overt rationale. The midwives in the SSPO study were asked not to use the interview schedules when they felt it was awkward or inadvisable to do so. It is important to note, however, that interviewing, as used in social science research, is often experienced as a supportive exercise by interviewees.*[10]

‖ *Further analysis of data pertaining to these important issues will be carried out and published elsewhere.*

The Sample

Figure 11.2 shows the SSPO sample, together with the pregnancy outcomes. Of the 510 women who agreed to take part in the trial, 256 women were randomized to the intervention group and 254 to the control group. One intervention group woman proved to have been incorrectly entered; two women, one in each arm of the trial, moved and became inaccessible to the study. Five women were carrying twins which were not diagnosed until after recruitment to the trial; these women were excluded from the main analyses, as the SSPO study was mounted as a trial of social support in singleton pregnancy. Equal numbers of women in the intervention and control groups had terminations and spontaneous abortions. There were three stillbirths in the intervention group, three intrapartum stillbirths associated with abruptio placentas and one antepartum stillbirth due to placental insufficiency at 36 weeks (weight of 1,760 g). There were 240 live births in the intervention group and 243 in the control group. After allowing for five neonatal deaths, 238 intervention group and 240 control group babies remained at the end of the study period.

Table 11.2 shows the comparability of the two groups at entry to the trial. There was no difference in mean gestation at booking, the mother's age, smoking status at booking, or parity. A slightly higher percentage of the intervention group women were married or cohabiting. Approximately three-quarters of both groups were categorized as working class according to the present or previous occupation of the baby's father. One in five women had partners who were unemployed. About one-third of the women were themselves employed during pregnancy and similar proportions left school at or before 16 years of age. These are indications that the sample was disadvantaged socially as well as being at high risk obstetrically. There are no indications that the differences in pregnancy outcomes described below which favor the intervention group might reflect the fact that this group is less disadvantaged socially than the control group; if anything, the figures suggest that the opposite may be the case.

Results

Birthweight, Gestation, Labor, and Delivery

Table 11.3 gives mean birthweight. The initial aim of increasing birthweight by 150 g proved to be overambitious. Taking singleton babies who survived (the most important criterion from the mother's point of view), the difference between the intervention and control groups is 50 g. For live singleton births it is about the same, but the difference is less when the stillbirths are included. It is interesting to note that a recent overview by David Rush[1] of dietary interventions in pregnancy concluded that the overall birthweight effect of these interventions is in the range of 40–50 g.

From table 11.4 it can be seen that there were fewer LBW babies in the intervention group. Table 11.5 shows that our intervention had no effect on mean gestational age.

Tables 11.6–11.9 give the findings for the labor and delivery variables we identified at the outset as possible areas of effect—onset

of labor, mean length of labor, type of delivery, and analgesia/anaesthesia in labor. There are few differences here that are statistically significant in the accepted sense (the tables carry a *p* value where this is less than 0.1). It is clear, however, that the direction of almost all of these results is in favor of the intervention group.

Maternal Physical Health and Medical Care

Figures for some dimensions of the women's physical health in pregnancy and use of medical care are given in Tables 11.10–11.12. There is a suggestion in Table 11.11 that symptoms of hypertension were less common in the intervention group; these women also experienced fewer hospital admissions for threatened preterm labor. The lower incidence of tiredness and insomnia in the intervention group may be linked with the lower incidence of depression in pregnancy (see table 11.16). There was no difference in the incidence of medical diagnoses of intrauterine growth retardation or uses of cervical suture and betamimetics (see table 11.11). Fewer women in the intervention group received more than one ultrasound scan, and fewer had antenatal cardiotocography. The most striking finding in these tables is the incidence of antenatal hospital admissions, which was significantly lower in the intervention group.

Table 11.12 provides data on the period after birth. There were significant differences between the two groups, with 70 percent of the intervention women, compared with 60 percent of the control women, reporting their own health as good or very good. In response to the question of whether or not there are continuing physical problems as a result of the birth, there is also a difference between the two groups.

Finally, fewer intervention group women made use of the health services (apart from their routine postnatal check-up), and there was a significant difference in the use of primary health care.

Baby's Condition

Tables 11.13–11.15 relate to the condition of the baby. There was some difference observed in terms of Apgar scores. About the same number of babies in each group were resuscitated, but there was a statistically significant distinction in the methods used. Intervention group babies were more likely to have their airways cleared and/or simple suction, and control group babies were more likely to need oxygen or more invasive methods of resuscitation (see table 11.13). Approximately the same number of babies in the two groups went to the neonatal unit; however, there were some differences in the care received within the neonatal unit, with control babies using more. Method of feeding at discharge from the hospital also tended to differ (see table 11.14). According to their mothers, intervention group babies were somewhat healthier than control group babies. This appears to be reflected in the figures for babies' health service use after birth, which parallel the findings of the mothers. A significantly greater proportion of the intervention group babies were not health service users. About the same proportions were still in or had been readmitted to the hospital, but intervention babies were taken back to the hospital somewhat less than the others (see table 11.15).

Psychosocial Outcomes

Information on psychosocial outcomes is taken mainly from the postnatal questionnaire. According to table 11.16, the most statistically significant difference from this point of view between intervention and control group women lies in the area of "worries" about the baby after birth. Measures of perceived control over one's life and depression (taken in the hospital after delivery) also favor the intervention group, as indeed do all of the outcome measures shown in this table. Table 11.17 demonstrates what might be regarded as a serendipitous effect of the intervention, which was to increase the domestic participation of men in pregnancy and in the early weeks of parenthood.

Conclusion

This paper presents some of the initial findings from an RCT of a social support intervention in high-risk pregnancy. On the basis of these data, it can be said that there is no evidence that this intervention did any harm to the mothers and babies who received it, and a good deal of evidence that the effects were beneficial. Tables 11.18 and 11.19 give some summary measures of the way in which the SSPO intervention was seen by the supporters and by those supported. Listening was the single most valued characteristic attributed to the research midwives. As one woman remarked:

> . . . This time I've been lucky, because I've been able to talk, and I mean I've got a lot of fears and anxieties in my mind that I've been able to tell you about, that I wouldn't have been able to talk about to a doctor. . . . I have been looking forward to you coming. I've been saying that woman is coming on Wednesday. . . .[12]

Research midwife, protesting:

> "I'm not THAT WOMAN, I'm Susan."
>
> "I mean I can talk about it to my friends and that, but it's just that little bit of extra professional help. . . ."

The help that the research midwives in the SSPO study were able to give has to be seen in the context of women's ordinary experiences with maternity services. In both Europe and North America, there is convincing evidence that these services are frequently felt by mothers to be unsupportive and demoralizing.[12,13] Poor doctor-patient communication was often commented on in the SSPO study, as it was by this woman discussing a previous stillbirth:

> . . . There's a lot of questions you want to ask . . . but you just can't. Everything is rushed and you can't think (properly) . . . and when you do ask them, you think you're being silly because they try to put you off. . . . When we lost the last baby, I had to go there for the postnatal and we thought it was for the results of the postmortem . . . and (the doctor) said, 'Why have you come? What have you come for?' So I said, 'I don't know, I think I've come for the results of the postmortem,' . . . and he said, 'Don't you know why your baby died then?' And I said, 'No,' . . . and he said, 'Oh well, at 25 weeks, what do you expect?' and passed it off. . . .

Many of these women had unresolved problems to do with their past experience of giving birth to a LBW baby; for some, it was the first time they had been given the opportunity to discuss their feelings fully with anyone. It would thus seem that the therapeutic effect of a social support intervention in the pregnancies of such women may have as much to do with the reconstruction of the meaning of past experiences as with the mediation of present experiences. It is salutary to note (see table 11.19) that the importance of the supporters' help in these circumstances may often be undervalued by the supporters themselves, who may feel skeptical about the potential of the modest help they are able to give in counteracting the effects of the multiple social deprivation which affects the lives of many urban families in the 1980s.

ACKNOWLEDGMENTS

We are grateful to the DHSS for supporting the SSPO study. Particular thanks are due to Sandra Stone for preparing the manuscript, and to Penrose Robertson for his computing expertise.

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Statistical Findings: The Social Support and Pregnancy Outcome Study

Figure 11.1
Consent, Randomization, and Data Collection Procedures

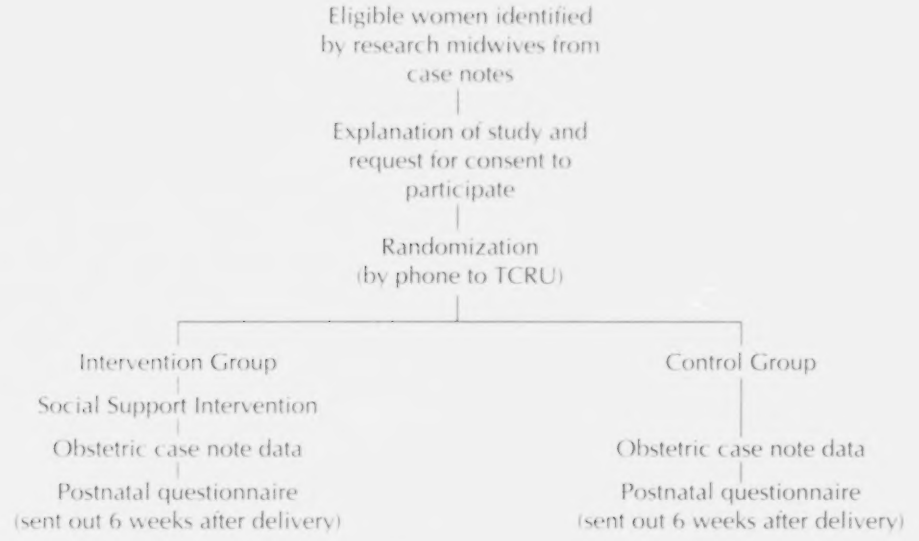
Eligible women identified by research midwives from case notes
Explanation of study and request for consent to participate
Randomization (by phone to TCRU)
Intervention Group
Social Support Intervention
Obstetric case note data
Postnatal questionnaire (sent out 6 weeks after delivery)
Control Group
Obstetric case note data
Postnatal questionnaire (sent out 6 weeks after delivery)

Figure 11.2
Study Sample and Pregnancy Outcome by Assignment into Intervention and Control

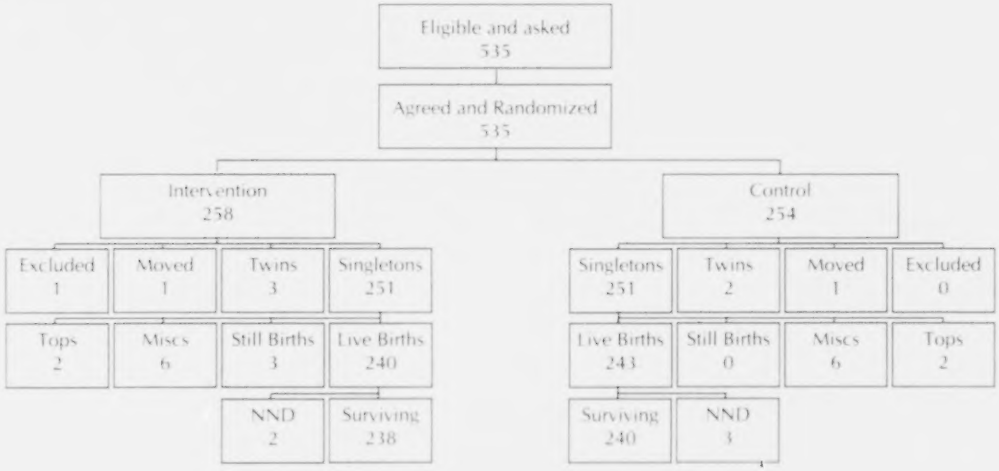

Table 11.1
Structure and Content of the SSPO Intervention

Mean gestational age (weeks) at:	
1st home contact	17.8
2nd home contact	24.0
3rd home contact	29.7
1st telephone contact	22.3
2nd telephone contact	27.3

Women who received:	percentage	number
minimum social support package	5	12
less than minimum social support package	25	61
more than minimum social support package	70	170
No referral of any kind	22	54
Referred to:		
health professional(s)	52	125
welfare agencies	27	64
No lifestyle information given	34	81
Given information about:		
smoking	12	28
alcohol	8	18
diet	24	58

Table 11.2
Comparability of Groups at Recruitment to Trial

	Intervention	Control
Mean gestation (weeks)	15.7	15.6
Mother's age (years)	27.9	28.1
Percentage of group:		
Under 20 years of age	4	4
Married/cohabiting	84	81
Working class*	77	72
Partner unemployed*	21	20
Employed during pregnancy*	33	35
Education completed at or before 16 years of age. *	31	31
Smoking at time of enrollment	41	40
Parity	1.8	1.8
Mean number of previous LBW deliveries:		
1	85%	86%
2	11%	12%
3 +	4%	2%
Total Numbers	255	254

** Information taken from postnatal questionnaires.*

Table 11.3
Mean Birthweight

	Intervention	Control
Surviving singletons	2973.9 g (*N*=238)	2923.1 g (*N*=240)
Live singleton births	2956.3 g (*N*=240)	2906.5 g (*N*=243)
Singleton live and stillbirths	2944.4 g (*N*=243)	2906.5 g (*N*=243)

Table 11.4
Low Birthweight

	Intervention		Control	
	percentage	number	percentage	number
Live Singleton Births				
< 2500 g	17	42	21	52
>2500 g	83	198	79	191
Total	100	240	100	243
Singleton live and stillbirths				
< 2500 g	19	45	21	52
> 2500 g	81	198	79	191
Total	100	243	100	243

Table 11.5
Gestation at Delivery

	Intervention	Control
Mean gestational age at delivery (weeks)	38.2	38.2
Percentage of deliveries:		
< 28 weeks	3.6	3.2
< 37 weeks	19.3	20.5
Total numbers (all pregnancies except for terminations)	249	249

Table 11.6
Onset of Labor

	Intervention		Control	
	percentage	number	percentage	number
Spontaneous	74	180	68	163
Elective	22	53	26	64
Emergency cesarean	4	10	6	14
Total*	100	243	100	241

**All singleton live births and stillbirths for which information was available.*

Table 11.7
Mean Length of Labor

	Intervention	Control
First stage (hours)	5.3	5.4
Second stage (minutes)	20.4	21.1
Third stage (minutes)	10.0	7.2
Total* (hours)	5.7	5.9

** Based on N=202 (Intervention) and N=193 (Control), live and stillbirths, non-cesarean-delivered mothers, for whom information was available.*

Table 11.8
Type of Delivery

	Intervention		Control	
	percentage	number	percentage	number
Spontaneous	81	197	75	182
Forceps/vacuum extraction	2	5	5	11
Cesarean section	17	41	21	50
Total*	100	243	100	243

**All singleton live births and stillbirths for which information was available.*

Table 11.9
Analgesia/Anesthesia in Labor

	Intervention		Control	
	percentage	number	percentage	number
None/Entonox	45	108	40	95
Pethidine	26	162	26	61
Epidural	11	27	16	39
GA	17	41	18	43
Other	1	3	0	0
Total*	100	241	100	238

**All singleton live births and stillbirths for which information was available.*

Table 11.10
Maternal Physical Health in Pregnancy

	Intervention percentage	Intervention number	Control percentage	Control number
Proteinuria				
on own	24	51	27	64
with bp	8	8	11	11
Suspected IUGR	21	51	22	54
Threatened miscarriage*	6	14	9	20
Admitted for threatened pre-term labour	14	34	18	43
Tiredness*	78	180	83	187
Insomnia*	22	50	27	62
Swollen ankles*	26	59	32	73

** Mother's information*

Table 11.11
Medical Care in Pregnancy

	Intervention percentage	Intervention number	Control percentage	Control number
Cervical suture	4	9	4	13
Betamimetics	3	8	4	10
More than one ultrasound scan	73	178	77	187
Antenatal CTG	40	97	49	118
				$p < .06$
Mean number of hospital visits	5.1		5.1	
Admitted to hospital antenatally	41	97	52	126
				$p < .01$
Mean number of days in hospital antenatally*	7.2		8.3	

** Base for calculation is number of women admitted.*

Table 11.12
Maternal Physical Health After Birth

	Intervention percentage	Intervention number	Control percentage	Control number
Health very good/good	70	161	60	133
				$p < .03$
Has no physical problems now	59	69 ($N = 118$)*	46	52 ($N = 113$)*
No health service use (except for routine postnatal)	40	93	31	70
				$p < .05$
Still in/readmitted within 6 weeks of delivery	4	8	4	8
Hospital visit (excluding routine postnatal)	4	9	8	18
Visit to/from GP	29	67	39	88
				$p < .03$
Other	6	13	7	16

Based on $N = 230$ (Intervention) and $N = 226$ (Control) surviving singleton babies whose mothers returned postnatal questionnaire and answered relevant questions.

** Number who recorded any physical problem after the birth.*

Table 11.13
Baby's Condition After Birth

	Intervention percentage	Intervention number	Control percentage	Control number
Apgar: <7 at 1 min	12	29	15	35
<7 at 5 min	2	4	4	8
Not resuscitated	34	81	33	81
Cleared airways/ suction only	64	100	54	83
O_2 by bag and mask/ other resuscitation	32	50	38	59
Endotracheal intubation	5	7	9	13
		($N = 157$)		($N = 155$)

$p < .04$ for resuscitation method.

Based on singleton live births for which information on Apgar scores/resuscitation was available.

Table 11.14
Baby's Care After Birth

	Intervention		Control	
	percentage	number	percentage	number
To neonatal unit	15	35	15	37
Mean number of days		9.6		17.1
Ventilated	3	8	5	13
Mean number of days		5.0		6.18
Supplemental O_2	3	8	5	13
Mean number of days		3.85		10.08
Totally intravenously/ tube fed	5	13	5	13
Mean number of days		6.62		18.62
Breastfed at discharge*	45	105	39	89

Based on N = 240 (Intervention) and N = 243 (Control), all singleton live births. Means in each case based on number receiving the procedure; figures exclude 1 baby who died in neonatal unit and 8 who are still in.

** Survivors for whom information available (N = 230 for Intervention and N = 226 for Control).*

Table 11.15
Baby's Health After Birth

	Intervention		Control	
	percentage	number	percentage	number
No problems after discharge	74	157	66	142
				$p < .07$
No health service use	35	81	24	54
				$p < .007$
Still in/readmitted to hospital	7	16	7	15
Hospital visit	11	24	16	35
Visit to/from GP	45	104	43	98
Other	13	29	13	30

Based on N = 230 (Intervention) and N = 226 (Control) surviving singleton babies whose mothers returned postnatal questionnaire and answered relevant questions.

Table 11.16
Psychosocial Outcomes

	Intervention		Control	
	percentage	number	percentage	number
Enjoyed birth	66	151	58	130
				$p < .08$
'Excellent' relationship with baby now	64	148	60	134
Depressed in pregnancy	14	31	18	40
Depressed after birth	40	92	48	107
				$p < .08$
Control over life	72	166	63	143
				$p < .08$
Worried about baby now	16	36	28	63
				$p < .001$

Based on N = 230 (Intervention) and N = 226 (Control), mothers of surviving singleton babies who returned postnatal questionnaire and answered relevant questions.

Table 11.17
Partner's Support and Help During Pregnancy, Birth, and After Birth

	Intervention		Control	
	percentage	number	percentage	number
Present during labor	78	177	76	171
'Took days off' very often/often 'to be with you' during pregnancy	30	56	27	47
In pregnancy helped very often/often with:				
shopping	85	187	77	161
				$p < .01$
other children	94	191	89	173
				$p < .05$
After birth helped very often/often with:				
shopping	88	189	81	169
				$p < .02$
other children	97	197	92	178
				$p < .05$

Based on N = 230 (Intervention) and N = 226 (Control) mothers who returned the postal questionnaire and answered relevant questions.

Table 11.18
Attitudes Toward the Intervention

Percentage of women who said it was important that:

She listened	80%
She gave advice	65%
I saw her throughout pregnancy	56%
She gave information	56%
She was a midwife	33%

Total N = 236

Table 11.19
Value of Contact with Midwife in Pregnancy

	Very/particularly helpful	Quite helpful	Other/no information
Midwife considered herself*	13%	42%	45%
Woman considered midwife†	50%	44%	6%

* *Mean of 3 home contact assessments.*

† *From postnatal questionnaire.*

Prevention of Preterm Deliveries By Home Visiting System: Results of a French Randomized Controlled Trial

Beatrice Blondel, M.D.
Jospha Llado
Gerard Bréart, M.D.

The Home Visiting System

In France, the home visiting system is a part of Maternal and Child Health Services, a program created after the Second World War to reduce infant mortality and to promote the health of mothers and children under six years of age. Through clinics and home visits, Maternal and Child Health Services provide health care, screening, and immunization free of cost. The program is staffed by multidisciplinary teams consisting of doctors, midwives, nurses, nursery nurses, and social workers.

During the 1960s, home visits were made by nursery nurses to children only. A home

visiting system for pregnant women was later introduced as part of a national program which began in 1970 and which intended to reduce perinatal mortality and the incidence of handicapped infants.[1] It included allocation of financial resources to develop health services; educational programs; and regulations to improve maternity unit equipment, prenatal care, and the working conditions of employed women. The first domiciliary midwife began visiting pregnant women who were registered at Antoine Beclere Hospital (Department of Dr. Emile Papiernik) in 1975. At present, between 500 and 600 midwives make home visits in France.

The activities of the domiciliary midwives are not defined precisely. In accordance with the regulation, home visits should be offered to two specific high-risk populations: Women who have difficult life circumstances, and women who have pregnancy complications. For the first group, the home visiting system is considered as a means of reaching women who are reluctant to use health services, improving women's health habits, encouraging their relatives and friends to help them with housework, and establishing a link between the families and agencies employing home helpers. For the second group of women, the task of the midwives is to monitor pregnancy complications. Routine medical examination includes measurement of blood pressure, analysis of urine glucose and protein, measurement of fundal height, monitoring of fetal heart rate and fetal movements, and assessment of cervical state. Domiciliary midwives are not allowed to prescribe drugs.

High-risk women who receive home visits also have routine visits at prenatal clinics. Home visits are free for every pregnant woman.

The importance of the two basic activities of domiciliary midwives—support and care—varies according to geographical area. In Paris, supervision of pregnancy complications is the main activity. In 1982, 80 percent of the pregnant women received home visits because they had a threatened preterm labor; the other indications were hypertension, intrauterine growth retardation, and multiple gestation. In Paris, each midwife works closely with one maternity unit and visits pregnant women who attend the outpatient clinic of this unit.

Background and Aim of the Study

Two randomized controlled trials (RCTs) were conducted to study the effectiveness of routine home visits during pregnancy. Olds et al. evaluated a program of prenatal and postnatal home visits among socially disadvantaged women in New York State.[2] Nurses made an average of nine visits from the beginning of pregnancy until delivery. Their activities included parent education, enhancement of the women's informal support systems, and linkage of the parents with community services. A French RCT was conducted during the same period (1978–1980), but in this study women were visited at home when they had pregnancy complications. Seventy percent of the women were at high risk for preterm labor.[3] Midwives made an average of six visits from the onset of the complication to delivery. Both of these studies failed to demonstrate any decrease in

low birthweight and preterm delivery rates among the overall population, and a significantly higher perinatal mortality rate was observed in the intervention group in the French trial.

The publication of the French trial raised several questions concerning the effectiveness of home visits and the benefits which could be expected from this care system. The higher risk of perinatal mortality associated with the home visits could be explained by the inclusion criteria used in the trial: It was conducted only a few years after creation of the home visiting system, health benefits may have been overestimated, and some high-risk women should not have been enrolled in the trial.

Moreover, against the French background, it may be difficult to show any health benefits of home visits on pregnancy outcome in cases of threatened preterm labor because there is a very active management of this complication in France and we can expect a high level of care among women visited at home and women attending prenatal clinics.

If the chance to show a health benefit is small, other effects of home visits should be considered (mainly, the cost of medical care and the women's view). Policymakers might be interested in this medical care arrangement if it reduces the overall cost of care during pregnancy, especially the costs related to hospitalization. The choice of a pattern of medical care should not be based on financial reasons only, however; the women's views of prenatal care arrangements also should be taken into account. The aims of our study were to ascertain if a home visiting system reduces the cost of medical care during pregnancy and if the women's satisfaction with medical care is greater when they have experienced home visits as compared with the usual care provided in the outpatient clinics.

Method

The study design consisted of a randomized controlled trial. The protocol and questionnaires were prepared with the domiciliary midwives who were working in Paris.

The study was restricted to women who had threatened preterm labor because it was the main indication for prescribing home visits. The eligibility criteria were defined according to the usual practice in Paris: Women were recruited if they had a moderate threatened preterm labor, and women who received intravenous betamimetics were excluded because these drugs are administered for acute threatened preterm labor in hospital exclusively. Women were enrolled between 26 and 36 weeks of gestation.

Two groups of women were compared. Women in the intervention group were provided one or two home visits per week; in addition, women had access to the domiciliary midwives by phone calls. Considering that the aim of this study was to assess the existing home visiting system, the intervention was conducted by the present midwives without any extra intervention. No home visit was provided to women of the control group. Women in both groups received routine prenatal care from obstetricians or midwives at the outpatient clinics, and they were hospitalized if necessary.

The women were allocated into the inter-

vention group and the control group by randomization with sealed envelopes; this randomization occurred in two different settings: (1) In the outpatient clinic, when a threatened preterm labor was diagnosed during a prenatal visit; and (2) in the inpatient ward, when the risk of preterm delivery of a hospitalized woman was decreasing and the discharge was considered.

The sample size estimation was based on the number of hospital days during pregnancy, which is the main part of medical cost before delivery. The number of women required for the study was estimated to be 90 in each group. This size should enable us to detect a statistically significant reduction of number of days in hospital equivalent to 50 percent of the standard deviation; this standard deviation was determined from observational studies conducted in France. The probability of observing a true difference between the two groups was 95 percent.

The study was carried out in four maternity units of the public and private sector located in Paris: Hospital of the Deacons, Notre Dame of Bonsecours Hospital, Saint Anthony's Hospital, and Tenon Hospital. The first women were enrolled in November 1985 and the last women delivered in August 1987. Data collection was needed at different points in the study. A sheet was completed at study entry to ascertain the eligibility of each woman and to assess the risk of preterm delivery according to the state of the cervix and the frequency of contractions. After delivery, a questionnaire was given three to four days after birth, when the woman was still in the maternity unit. It was a self-administered questionnaire, which focused on the women's views of prenatal care arrangement and inquired about the medical knowledge of the women, bed rest, and support during the last trimester of the pregnancy. Data on prenatal care, delivery, and pregnancy outcome were collected from medical records by one or two midwives in each hospital.

Statistical analysis was carried out by the use of X^2 and t tests, as appropriate.

Results

A total of 158 women were randomized into either the intervention or the control group. Six women were lost to follow-up after enrollment; it was impossible to identify these women and to know whether they differed from the other women. The following results are based on 79 women in the intervention group and 73 women in the control group.

Compliance with the allocation was assessed. Four women in the intervention group had no home visit. Two of them were hospitalized several days after allocation, and they stayed in the hospital a long time. In the control group, eight women had home visits; they might have a higher risk of preterm delivery than the other women. Six women were hospitalized after randomization. For the analysis, we retained the groups as they were originally allocated.

In the intervention group, the midwives made an average of 4.6 home visits. The average length of the home visiting service was 30 days. In general, the last visit occurred during the 35th or 36th week of gestation.

At study entry, the intervention group and

the control group were similar on the major sociodemographic characteristics (see table 12.1). The distribution of age and parity was the same; the proportion of women who were married or who were cohabiting with the child's father and the proportion of women with French citizenship did not differ significantly. Furthermore, both groups had the same social class distribution.

The distribution of risk factors for preterm delivery was similar in the two groups. The proportion of women who had had a previous preterm delivery was 5 percent in the intervention group and 8 percent in the control group; this difference was not significant. At study entry, 77 percent of the women were perceiving contractions in the intervention group versus 79 percent in the control group (see table 12.2). A vaginal examination was carried out for every woman before enrollment. Dilatation of the internal os and short cervix were less frequent among the intervention group, and soft cervix and middle position of the cervix was more frequent in this group; nevertheless, none of these characteristics of the cervical state differed significantly in both groups.

The proportion of women who delivered before 37 weeks of gestation was 18 percent in the intervention group and 15 percent in the control group. Two perinatal deaths were observed in the intervention group and one in the control group; these three deaths occurred among premature babies whose gestational age at birth was 32 or 33 weeks and whose birthweight was between 1700 and 1800 g. These results show that the study population had a high risk of preterm delivery; in the control group, the preterm delivery rate was three times higher than it was in Paris in 1981.[1]

The trial was designed to assess the cost of medical care during pregnancy mainly through the cost of hospitalizations. The proportion of admissions to hospital was slightly higher in the intervention group than in the control group, and the mean stay in hospital was a little longer in the intervention group; however, none of these differences was significant (see table 12.3). The difference (intervention group minus control group) of the mean stay in hospital was 1.4 days (CI = - 0.8, + 3.5); the confidence interval included a range of situations, from a reduction of about 1 day in hospital through the home visiting system up to an increase of 3.5 days. Thus, the chance of reducing the cost of medical care related to hospitalization was very small.

The home visiting system nevertheless reduced the number of prenatal visits at the outpatient clinic, and the difference was significant: 33 percent of the women in the intervention group had 4 prenatal visits or more, compared to 54 percent of the women in the control group. All of the women except two were treated with tocolytic agents after study entry; the treatment was similar in both groups.

After delivery, we asked mothers whether they had been satisfied with their medical care when they had had a threatened preterm labor. Four answers were proposed: Very satisfied, satisfied, unsatisfied, and very unsatisfied. No woman was unsatisfied or very unsatisfied in the intervention group, and 3 women were unsatisfied or very unsatisfied in the control group. The proportion of very satisfied

women was much higher in the intervention group (78%) than in the control group (44%), and the difference was significant (see table 12.4). Another question was related to the prenatal care arrangement: "According to you, what is the best prenatal care arrangement when a threatened preterm labor is diagnosed?" The home visiting system was preferred more frequently than the other arrangements in both groups, but the proportion of women who preferred the home visiting system was 89 percent in the intervention group and 60 percent in the control group. The proportion of women who would have preferred hospitalization was similar in both groups; none of the women in the intervention group preferred numerous prenatal visits at the outpatient clinic, but 26 percent of the women in the control group did.

One of the tasks of domiciliary midwives is to provide information and support, with the objective of reducing tiring living conditions, improving home help, and encouraging women to have rest.

Bedrest was more frequently recommended among the intervention group than among the control group. Seventy percent of the women in the intervention group were asked to stay in bed the whole day, compared with 58 percent of the women in the control group, but this difference was not significant (see table 12.5). The women in the intervention group were taught to identify contractions more frequently than the women in the control group. This difference was statistically significant. In fact, the proportion of women who stayed in bed the whole day was higher (58%) in the intervention group than in the control group (42%) (see table 12.6); the difference was not significant, but the *p* value was 0.07.

In general, the women in the intervention group had more help than the women in the control group: 86 percent of the women in the intervention group, versus 70 percent in the control group, said that the amount of help had been higher during the episode of threatened preterm labor than during the first trimester of pregnancy. In the intervention group, 56 percent of the women who had previous children did not participate at all in child care; this proportion was 30 percent in the control group, and the difference was significant. The number of people who took responsibility of home tasks was nevertheless not different in both groups.

Conclusions

Women's satisfaction with medical care was much more important in the intervention group than in the control group. Satisfaction may have long-term effects on such outcomes as postpartum depression or mother-child relationship. Follow-up of the study population was not planned in our protocol, and we do not know the consequences of the women's satisfaction.

Several studies have reported that pregnant women are satisfied with whatever care they have experienced and prefer it to alternative possibilities. This statement was noted in relation to a new schedule of prenatal visits,[5] epidural,[6] continuous fetal heart monitoring during labor,[7] and early discharge after delivery.[8] It is not verified for home visits, how-

ever; in our study, at least 60 percent of the women in both groups preferred the home visiting system. In some cases, a new organization of medical care cannot be an improvement for the majority of the women; but, in general, women have difficulties considering the advantages and disadvantages of a new procedure or treatment which they have not experienced. Furthermore, differences between alternative possibilities sometimes mean very little. On the contrary, home visits may represent a real difference in care, tiredness, and relationship with midwives, and women who did not experience home visits could easily imagine how this system was managed.

This study does not show that the home visiting system reduced the number of days in hospital. In the best situation, there is a decrease of one day in the intervention group, but actually the cost of home visits per woman is almost equal to the cost of one day in hospital. Thus, in this hypothesis, medical cost is equivalent in both care systems. In the worst situation, the number of hospital days is much higher in the group of women visited at home than in the other group.

Against the background of medical practice in Paris, it seems difficult to reduce the number of days in hospital through the home visiting system. French obstetricians have a very active approach to threatened preterm labor, which includes high rates of hospitalization, and they may be reluctant to decrease this standard of care even if another prenatal care system is proposed. Furthermore, the domiciliary midwives who were involved in the trial could not interfere with admissions to hospital. The majority of the women were admitted on their own initiative, and only 14 percent of the hospitalizations were decided by the midwives during a home visit. In addition, when a woman was admitted because of a threatened preterm labor, the medical staff may have been inclined to keep her at the hospital for at least three to five days, with the objective of prescribing a treatment and monitoring the complication over several days. In the trial, a short hospital stay was not more frequent in the group of women who received home visits than in the other group. In general, a greater number of visits may induce a greater number of medical interventions. Women who had home visits had about twice as many internal examinations as the other women; therefore, the chance to detect a complication was higher in the intervention group. Furthermore, women in this group were more aware of the signs of pregnancy complication than the other women and they might pay more attention to those signs.

The results on the number of days spent in the hospital depend on the local medical practice. In a previous trial, Spira et al. did not find any significant difference in the mean stay in the hospital,[1] but this study was carried out a short time after the creation of this care system, whereas several years are required to have an adjustment of current medical practice to an innovation. Therefore, it would be important to have results on more recent studies in other areas or in other maternity units.

This study was restricted to threatened preterm labor. It does not give any conclusion for other pregnancy complications which are supervised by domiciliary midwives, such as hypertension. It also does not give any conclu-

sions for another type of care which is provided by domiciliary midwives: Out of large towns, the midwives provide home visits to socially disadvantaged women; their basic activity is to encourage women to attend prenatal clinic and to have regular rest and appropriate diet. The benefits of such care have not yet been assessed in France. Research on the effects of home visits among underprivileged women should be considered in the future.

Acknowledgments

This study was supported by grants from the Ministre des Affaires Sociales et de l'Emploi (Direction Generale de la Sante). We thank the chiefs of the four Departments of Obstetrics and Gynecology for permission to carry out the trial. Our thanks also go to Marieciel Allard, Dominique Decoudun, Marie-Paule Leloup, Dominique Lignac, and Frederique Teurnier, who are domiciliary midwives in Paris, for their help in preparing the protocol and the questionnaires. We wish to thank Marie-Christine Nourry for preparation of the manuscript.

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Statistical Findings: Prevention of Preterm Deliveries by Home Visiting System

Table 12.1
Maternal Demographic and Social Characteristics

	Intervention group percentage (N = 79)	Control group percentage (N = 73)	*p*
Age (years)			
≤ 24	25	18	
25–29	34	37	NS
≥ 30	41	45	
Parity			
0	49	49	
1	36	40	NS
2 or more	15	11	
Fr. citizenship	20	30	NS
Married or cohabiting with the child's father	91	93	NS
Social class*			
I	31	30	
II	23	15	
III	17	27	NS
IV	29	28	

* According to occupation of the child's father; women who were living alone were excluded.

I: managers, engineers, professional workers.

IV: manual workers, unemployed.

Table 12.2
Contractions and Cervical State at Study Entry

	Intervention group percentage	Control group percentage	*p*
Perceived contractions	77	79	NS
Cervical Dilation			
no	5	6	
external os	46	40	NS
internal os	49	54	
Length of the cervix (cm)			
≤ 1	35	30	
2	52	54	NS
≥ 3	13	16	
Consistency			
firm	23	26	
medium	41	46	NS
soft	36	28	
Position			
posterior	57	59	
mid	42	38	NS
anterior	1	3	
Low station	4	1	NS
Expansion of the lower uterine segment	79	79	NS

Table 12.3
Prenatal Care After Study Entry

	Intervention group	Control group	*p*
Percentage admitted to hospital	45	36	NS
Total number of hospital days*			
Hospitalized women	9.4 ± 8.2	8.3 ± 8.8	NS
all women	4.3 ± 7.2	2.9 ± 6.6	NS
Prenatal visits at outpatient clinic (percentage)			
0–1	27	10	
2–3	40	36	NS
4 or more	33	54	

* *mean ± s.d.*

Table 12.4
Mother's Views of Prenatal Care

	Intervention group percentage	Control group percentage	*p*
Were you satisfied with your prenatal care since you had a threatened preterm labour ?			
very satisfied	78	44	
quite satisfied	22	51	< 0.001
unsatisfied or very unsatisfied	0	5	
According to you, what is the best prenatal care arrangement when a threatened preterm labor is diagnosed ?			
hospitalization	11	15	
more visits at the outpatient clinic	0	26	< 0.001
home visits by a midwife	89	60	

Table 12.5
Information about contractions and bedrest

	Intervention group percentage	Control group percentage	*p*
Identification of contractions	77	59	< 0.05
Stay in bed			
no recommendation	9	18	
some hours	21	24	NS
the whole day	70	58	

Table 12.6
Bedrest and Home Help

	Intervention group percentage	Control group percentage	*p*
Bedrest during the whole day	58	42	0.07
More help than during the first trimester	86	70	< 0.05
Number of people who participate in house work			
0–1	53	60	
2	32	32	NS
3 or more	15	7	
Child care by the father or another person exclusively *	56	30	< 0.05

* *Multiparae only*

Smoking Interventions During Pregnancy

MARY J. SEXTON, PH.D., M.P.H.

INTRODUCTION

In this paper, three issues are addressed: (1) The importance of cigarette smoking during pregnancy as a risk factor; (2) the causality of cigarette smoking in reduced birthweight; and (3) the effectiveness of smoking cessation assistance in achieving abstinence. The discussions below often overlap at least two of these issues.

THE IMPORTANCE OF SMOKING AS A RISK FACTOR

The 1985 Institute of Medicine report[1] synthesized a large number of studies in the area of low birthweight. To organize the findings and discussions, risk factors were divided into the following categories: Demographic risk factors, medical risk factors that predate the current pregnancy, medical risk factors during the current pregnancy, behavioral and environmental risk factors, and health care factors. The data in

table 13.1 were abstracted from information presented in that report. For each broad category of risk, the table shows the specific factor for which the literature showed the largest relative risk for babies with intrauterine growth retardation (IUGR). Some estimates of relative risk were less reliable than others, and this was indicated by a range of estimates. In general, however, the largest single risk factor within each of these categories showed a relative risk of about twofold or threefold. Smoking had about the same level of relative risk as most other factors. The data showed that smokers are at three times the risk of having an IUGR baby; the increased risk associated with smoking is, overall, as high as for other risk factors for IUGR.

Only a few studies have used either IUGR or preterm delivery as the dependent variable, compared with a much larger number of studies that have examined average birthweight or low birthweight. The reason for concentrating on the IUGR relative risk, however, is that the work of Sexton and Hebel,[2] as well as others, supports the hypothesis that maternal smoking during pregnancy results primarily in a problem of intrauterine growth retardation.

In addition to the high level of increased risk, the importance of smoking in relation to birthweight from a public health point of view is further underscored by its prevalence. Over one-fourth of all pregnancies begin with the woman smoking; of these, only a fairly modest percentage of women quit on their own and continue their abstinence throughout the pregnancy.[3]

The Importance of Smoking as a Causal Factor

In assessing the risk associated with smoking from a clinical point of view, a major consideration is the extent to which the observed reduction in growth of the fetus is causal and the extent to which it can be reversed. If smoking is causally related to birthweight, its importance is much more significant. Over the last three decades, hundreds, if not thousands, of studies have replicated Simpson's earlier observation that maternal smoking is related to the birthweight of the infant.[4] Despite the overwhelming consistency of the data, a hotly debated issue arose almost immediately and has continued regarding whether smoking is truly causal since smokers were known to have, or more often just suspected of having, characteristics other than smoking that could account for the lower birthweight of their infants.[5] Arguments against smoking as a causal factor could best be refuted or supported by experimental evidence.

Results from Three RCTs on Birthweight

There have been only three randomized clinical trials (RCTs) reported on smoking cessation and birthweight. One has reported no difference; one, a statistically significant difference; and the latest, a difference in the expected direction, but not a statistically significant one. Despite the need for such experimental evidence to clarify the issue of causality, it was not until 1978 that Donovan reported results from his randomized clinical trial of smoking intervention and birthweight conducted in England.[6] His trial showed no difference in the birthweight of the babies born to the two randomly allocated groups of pregnant smokers. The intervention group had, on average, babies who weighed 12 g less than babies born to mothers in the control group. Some of the details of the

Donovan trial will be discussed later.

The second of the three randomized clinical trials that have examined birthweight is that of Sexton and Hebel.[2] It is the only reported randomized trial that has been conducted with a U.S. population, although it should be noted that two additional U.S. trials with plans to examine birth outcomes have been initiated. The first is a trial conducted at Kaiser Permanente in Oregon, in which the investigators intended to examine birthweight, but did not do so (probably because of the poor results obtained in quit rates).[7] The second is an ongoing trial in Vermont under the direction of Secker-Walker.[8] Birth outcomes have been collected; but although there are plans to examine them, there has not yet been a report.

The Sexton and Hebel study was designed to test the causal hypothesis that a reduction in smoking during pregnancy would increase the average birthweight of the infant. It is the only one of the three trials that has found a significant difference in quit rates and birthweights. Thus, the details of this trial are of special interest. With the cooperation of more than 50 private obstetricians in the Baltimore metropolitan area, 935 pregnant smokers were enrolled. The pregnant women filled out a brief questionnaire with information related to smoking and last menstrual period, and stated their willingness to be contacted by project staff. From these responses, eligibility was determined: Smokers of 10 or more cigarettes at the beginning of pregnancy were eligible (regardless of whether they were currently smoking or not) if they had not passed the 18th week of gestation. Because of expected high rates of recidivism, smokers who had quit prior to registration for care (baseline quitters) were included in the trial. The eligibles were contacted and a baseline visit scheduled. At that visit, written consent to participate and a questionnaire were obtained; a sample of saliva was also obtained, from which salivary thiocyanate was measured (thiocyanate is correlated with smoking status).[9] The smokers were randomly allocated to either a treatment or a control group.

On average, the women were approximately 25 years of age, they had completed a little more than 12 years of schooling, and about 40 percent were black. About one-third had had no previous pregnancies, and they were, on average, at about 15 weeks' gestation.

The women smoked about a pack of cigarettes at the beginning of pregnancy, but had reduced this to about half at the time of randomization. The baseline level of salivary thiocyanate was comparable in the two groups. Both experimental groups were comparable at the time of randomization.

The antismoking intervention was given by project staff, outside the health care setting, with a variety of contacts, including one personal visit at the time of enrollment, a monthly phone call, and biweekly contact by mail (usually in the form of a newsletter).[10]

The smoker was provided health information on the risks to her own health and to that of her baby. The main assistance, however, was in the form of information on how to quit through suggestions and guidance in behavioral strategies. The smoking cessation counselors gave no information on caffeine, alcohol, nutrition, or weight gain. When a woman asked about these factors, she was told to talk with her physician. Discussion of these factors was

refrained from in an effort to keep the intervention purely an antismoking one.

Table 13.2 shows the results for the smoking information obtained at the 8th month of pregnancy. Twenty percent of the women in the control group quit smoking and 43 percent of the women in the treatment group ($p < 0.01$) reported that they had quit smoking. Consistent with the quit rates are the differences in the distribution of smoking between the two groups. The biochemical measurement, salivary thiocyanate, was also statistically different at a significant level. Thus, the several assessments showed a significant decrease in smoking for the intervention women.

The pregnancy outcomes for the two experimental groups were comparable; 96.7 percent of the control pregnancies resulted in a single live birth, as did 96.6 percent of the pregnancies in the intervention program. There was no indication of differential pregnancy loss for the two groups. The birthweight hypothesis was tested on 867 single live births. As shown in table 13.3, the babies in the control group weighed 3,186 g; those in the treatment group weighed, on average, 3,278 g ($p < 0.05$). Based on the evidence of the quit rates and the birthweights, the null hypothesis of no difference in average birthweight was rejected. The percentage of babies weighing less than 2500 g at birth is also shown; 8.9 percent of the control babies, compared with 6.8 percent of the treatment babies, were low birthweight babies. The percentages of babies weighing less than 1500 g was 1.1 for control babies and 1.9 for treatment babies. Neither of these last two comparisons was significantly different.

The most recently reported RCT is that of MacArthur, Newton, and Knox,[11] conducted in the United Kingdom. Mothers allocated to receive assistance with their smoking had babies weighing 34 g more, but this difference failed to reach statistical significance.

Comparisons of the Three RCTs

At first glance, the results of the three trials appear to be in conflict with each other; however, insight into the reason for the apparent differences is gained by examining some of the design and implementation features of the studies. Table 13.4 shows the birthweight results by the two experimental groups for the three randomized clinical trials. As stated earlier, the first trial, conducted by Donovan, showed no significant difference in birthweights between infants whose mothers were in the treatment group and those whose mothers were in the control group. The trial conducted by Sexton and Hebel showed a statistically significant difference of 92 g. MacArthur et al. found a difference of 34 g. The table also shows the quit rates achieved in the two more recent trials. Donovan has never reported the quit rates for his trial, but concluded that the difference between the two groups was modest at best and may not have differed at all.[5] In the latest trial, MacArthur et al. reported an increase of 3 percent in the quit rate in the treatment group compared to that of the control group (9% v. 6%). In the Maryland study, the difference in quit rates is reported to be 23 percent. If the women who had already quit before enrollment (baseline quitters) are excluded (for closer comparability with the MacArthur et al. study), the quit rates between the two experimental groups in the Maryland cohort still differ

substantially: 32 percent for the treatment group versus 7 percent for the control group. Thus, the failure to find birthweight differences in the two United Kingdom randomized clinical trials results directly from their not achieving large enough differences in the relative quit rates. The reason the quit rates were so radically different from the Maryland rates probably stems from the features of the studies.

Design Features of the Studies

Some of the design features of the three studies are shown on table 13.5.

Location

As indicated, two of the studies were conducted in the United Kingdom, one in London and one in Birmingham; the Sexton and Hebel study was conducted in Maryland. Cultural differences alone might explain the quit rates, but there seem to be other possibilities as well.

Smoking Status

Amount Smoked and Gestation at Enrollment

The smokers included in the studies varied. Donovan included smokers of any amount at the beginning of pregnancy if they were smoking five or more cigarettes at the time they were randomized into the study. The average gestational age of the women included in the trial was almost 16 weeks (he had included women up to 30 weeks of gestation.) Sexton and Hebel enrolled women who smoked more at the beginning of pregnancy (10 or more cigarettes), but because they had no cut-off regarding smoking at the time of enrollment, they included women who had already quit at the time of enrollment. MacArthur et al. enrolled all pregnant smokers at the time of booking regardless of the amount. The women enrolled in their study and in that of Sexton and Hebel were earlier in their gestation than the enrollees in the Donovan study, giving a little more time for intervention. The differences in the smoking criteria used for these three studies are reflected in the averages of the amount of smoking for those enrolled in the study. The women in the two United Kingdom studies smoked about 18 cigarettes per day at the time they became pregnant. The women in the Maryland study smoked over 20 cigarettes per day at the time they became pregnant, but were smoking only 11 cigarettes per day at the time of enrollment. Women in the two United Kingdom studies had to be smoking at the time of entry into the study, so there was not as great a reduction in the amount smoked between onset of pregnancy and entry into the study. If the baseline quitters are excluded from the Maryland cohort, the women smoked an average of 21.7 cigarettes at the beginning of pregnancy and decreased to 13.5 cigarettes by the time of registration for prenatal care (on average at 15 weeks' gestation). Thus, the Maryland study subjects at baseline had already reduced smoking to a lower level than seen in the two United Kingdom studies.

Assessment of Smoking

In the last column of table 13.5, it can be seen that the studies differed in the way in which smoking status at the end of pregnancy was determined. The two United Kingdom studies assessed the smoking status only after delivery by self-reported recall information. Neither reported any biochemical assessment of smoking. In the Maryland study, both self-

reported data and salivary thiocyanate were obtained prospectively. The different assessment of smoking rates introduces some uncertainty about the comparability of the data. Nevertheless, the differences in the amount smoked by the subjects in the three trials and the time the woman could be exposed to the intervention (gestational age at enrollment) do not seem great enough to account for the differing quit rates achieved in the studies.

Intervention

In addition to the differences in the amount of cigarettes smoked, other features of the three studies varied and are the ones most likely to explain the quit rates. These features relate to the intensity of the intervention sites and the intervention staff. The two United Kingdom studies were conducted within a small number of clinical settings, and the intervention was carried out by the clinic staff themselves. In the Maryland study, the smokers were recruited from a much larger number of practice settings, and the intervention was conducted outside of the practice setting by staff recruited and trained by the project. In the Birmingham study, the amount of time and attention given to the intervention varied from one staff member to another and at times was not conducted as planned. From discussions with both of the United Kingdom study groups, the antismoking intervention was, on average, relatively weak compared to the number of contacts, intensity, and time given in the Maryland study.

Allocation Scheme

There was also some possible compromise in the integrity of the two experimental groups from the studies being given in the clinical setting and implemented by the regular prenatal staff. In the Donovan study, the smokers were randomized on an individual allocation basis. In contrast, for practical reasons, the accrual of subjects for the MacArthur study was by four-week periods in which all smokers booking at the hospital received the intervention during a designated four-week interval followed by a four-week interval during which smokers received no intervention. The same clinic staff were responsible for patient care during the intervention and nonintervention phases.

The brief highlighting of some of the design differences among the three randomized clinical trials is helpful in identifying several possible explanations of why there was such a marked difference between the reported quit rates in the two United Kingdom studies and the quit rate in the Maryland study and the accompanying lack of difference in birthweight. The United Kingdom studies had a less intensive intervention than the Maryland study and had less control over the implementation of the intervention. Furthermore, the same clinic staff were in contact with both treatment and control smokers, providing the opportunity for contamination (although the modest quit rates for the control groups indicate that this was not a substantial problem). Since the United Kingdom studies did not include an objective assessment of smoking, such as cotinine, it is difficult to know what the precise magnitude of response to the intervention really was, but it was surely very low.

Although the two United Kingdom studies did not produce evidence to refute the null hypothesis, the most reasonable explanation for

14.)

this is because the intervention was not strong enough to achieve a substantial difference in quit rates. The birthweight hypothesis can be tested only if there is a difference in quit rates that is large enough to produce a birthweight difference. It is much more reasonable, therefore, to conclude that the two United Kingdom studies produced no evidence on whether smoking causes reduction in birthweight than to conclude that antismoking assistance has no effect on birthweight. The weight of evidence produced by the large number of observational studies and by the Maryland randomized clinical trial supports a causal effect on the birthweight of the baby from maternal smoking during pregnancy. If the mother quits smoking during pregnancy, her baby will, on average, have an increase in birthweight. It must be recognized, however, that, to date, there is still not a solid base of experimental results on which to rest this statement.

Subgroup Analyses

Regardless of whether an overall effect for the randomized clinical trial is found or not, some analysis is usually directed toward suggestions of differential effects among subgroups of subjects. These subgroup analyses have to be viewed as unplanned analyses and, therefore, caution must be appropriately exercised in their interpretation.

Parity

The Birmingham data were analyzed and reported by parity. A larger difference in quit rates was found between the treatment and control groups for nulliparous women. These smokers (see table 13.7) had quit rates of 14 percent and 7 percent, respectively, in the treatment group and control group. In contrast, the respective quit rates among multiparous women were 7 percent and 6 percent for the treatment and control groups. The pattern of birthweights was consistent with the pattern of quit rates. The nulliparous women in the treatment group had babies who weighed an average of 96 g more than the control group babies. These findings give further support to the causal role of cigarette smoking: An increase in quitting causes an increase in birthweight. They also suggest, however, that smoking cessation intervention has very little impact either on quit rates or birthweights when the smoker has already had a pregnancy. Similar Maryland data are shown at the bottom of table 7 for the same stratified groups. Among the nulliparous subjects, about 10 percent of the control group of women quit smoking and about 36 percent of the treatment group quit smoking. This represents a 26 percent difference in the quit rates between the two experimental groups. Unlike the MacArthur et al. finding, the quit rates also differed between the two groups of women who had had one or more previous pregnancies. The higher quit rates in the treatment group were consistent with the finding of heavier weight babies in the treatment group. The multiparous women in the treatment group had babies who averaged 3,275 g, an increase of 112 g compared with the control group babies. When the quit rates in the Vermont study were examined, they did not differ according to the number of previous pregnancies the smoker had. The self-reported quit rates were 14.7 percent and 14.1 percent, respec-

tively, for women with no previous pregnancy versus those with 1 or more.* While some groups of nulliparous women, such as those in the Birmingham study, may be more responsive to a smoking cessation intervention, it is not a consistent finding. Thus, the most reasonable conclusion at this time is that all women, regardless of their parity, will benefit from antismoking intervention both by achieving higher quit rates and increased birthweights of the babies.

Race

Because of the concern for the increased low birthweight rates among blacks, the Maryland data were examined to determine for blacks the extent of response to smoking cessation intervention and the extent of impact on birthweights of the babies. Very little information on quit rates, if any, has been reported separately for black and white pregnant females. On the one hand, black and white females, overall, smoke in about the same proportion—around 25–30 percent. On the other hand, black females smoke fewer cigarettes per day than their white counterparts.[12] Table 13.8 shows that for the 296 blacks in the Maryland cohort who were still smoking at time of enrollment, 39 percent of those in the treatment group quit smoking, compared with 6 percent in the control group. Not as many whites in the treatment group quit (only 28%). The quit rates for blacks and whites in the control group were similar. Thus, the intervention produced a larger increase in quitting among blacks compared with whites. It did not, however, produce a larger differential in birthweights. For blacks, the treatment women had babies who weighed, on average, 94 g more at birth. For whites, the treatment group babies averaged 136 g higher in weight. Nevertheless, both blacks and whites derived significant benefit from the antismoking intervention.

In summary, the birthweights in all three randomized clinical trials and in the subgroup analyses seem consistently to follow clearly the pattern of quit rates, providing additional confidence in the conclusion that maternal smoking does cause a significant decrease in birthweight.

Effectiveness of Smoking Cessation Assistance

Information from the three trials that have reported birthweights has already been presented on the differential quit rates between two randomly allocated groups (see table 13.4). Three additional randomized clinical trials have reported on quit rates, but have not reported on birthweights. These have all been conducted within the prenatal care setting but with different approaches to the intervention.[7,13,14] An indication of the type of program is shown. The Baric and Windsor studies had a fairly modest level of intervention, consisting of self-help materials on smoking and a health message given in the Baric study by the physician or nurse and in the Windsor study by a health educator. The approach in the ongoing Secker-Walker study is much more intensive than in the other two in terms of the frequency of contacts, length, and focus of the interven-

* Secker-Walker, R. H. personnal communication

tion. The quit rate for the treatment groups for each of the three studies is 14 percent (in the Windsor study, a second treatment group had a 6% quit rate). The quit rates in the control group varied from study to study, resulting in a differential between the two experimental groups of around 5–10 percent. It is not likely that, with the modest differentials in quit rates and the sample sizes, a significant difference in birthweights would be found. These studies do show, however, that a modest level of intervention can increase the rate of quitting. Overall, the highest quit rates were produced in the Maryland study, with a 25 percent differential in the quit rates found. Even in that study, a very large proportion of smokers did not quit.

From the small number of randomized trials that have reported smoking and birthweight, there is room for optimism. Assistance to the pregnant smoker after she has registered for prenatal care can be effective in raising the proportion who quit and in increasing the baby's birthweight. There is still much more to learn, however, about how to provide effective intervention for smoking cessation during and following pregnancy.

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Statistical Findings: Smoking Interventions During Pregnancy

Table 13.1
Estimates of Relative Risk for Principal IUGR Risk Factors

Risk Category	IUGR RR	Risk Category	IUGR RR
• Demographic: Black	2.4	• Medical—Current Pregnancy: Preeclampsia/Toxemia	2.3–15.8
• Medical—Predating Pregnancy: Previous IUGR Baby	2.9–7.98	• Behavioral and Environmental: Smoking	3.04
		• Health Care: Absent/Inadequate Prenatal Care	2.0

Source: Institute of Medicine. (1985). *Preventing low birth weight.* Washington, D.C.: National Academy Press.

Table 13.2
Smoking Characteristics of Control and Treatment Groups at Eighth Month of Pregnancy*

Percentage Reporting Smoking, Cigarettes/day†	Control Group	Treatment Group
N	395§	395
0	20.0	43.0
1–5	12.7	19.1
6–10	22.0	16.2
11–20	31.4	17.8
≥ 20	13.9	3.9
Mean ± SD¶	12.8 ± 11.5	6.4 ± 8.7

Thiocyanate, mole/L	Control Group	Treatment Group
N	389	380
Mean ± SD	2,452 ± 1,228	2,094 ± 1,209

* *Includes only women who had not been delivered by the eighth-month contact.*

† *Difference in distributions of numbers of cigarettes per day was statistically significant by Kolmogorov-Smirnov test ($p < .01$).*

§ *Data missing on two subjects.*

‖ *Data missing on five subjects.*

¶ *Difference in mean cigarettes smoked was statistically significant by Student's t test ($p < .01$).*

‡ *Difference in mean thiocyanate levels was statistically significant by Student's t test ($p < .01$).*

Table 13.3
Measurement of Status of Newborn*

	Control Group		Treatment Group		
	N	Mean ± SD	N	Mean ± SD	t
Primary factors					
Birthweight (grams)	438	3,186 ± 566	429	3,278 ± 627	2.28†
Percentage < 2,500	438	8.9	429	6.8	—
Percentage < 1,500	438	1.1	429	1.9	—

* *Includes only single, live births.* † $p < .05$ *by Student's t test.*

Table 13.4
Results of Three Randomized Clinical Trials

Randomized Clinical Trial	N	Birthweight (g)		Quit Rates	
		TX	Control	TX	Control
Donovan (1972)	552	3172	3184	*	*
Sexton/Hebel (1979)	867	3278	3186	43%	20%
Macarthur/Newton/Knox (1981)	982	3164	3130	9%	6%

* *Not Reported*

Table 13.5
Smoking and Gestational Characteristics by RCT's of Examining Birthweight

RCT	Number at Randomization	Eligibility on Smoking Status:		Amount Smoked at Time of:		Assessment of Late Pregnancy Smoking Status	Gestational Age at Entry
		at Pregnancy	at Randomization	Pregnancy	Randomization		
Donovan (London) 1972	549*	> 1	> 5	17.7	15.2	retrospective self-report	15.9
Sexton, Hebel (Maryland) 1979	935	> 10	**	20.8	11.2	prospective self-report thiocyanate	15.0
Macarthur, Newton, Knox (Birmingham, UK) 1981	1156	**	> 1	18.2	14.1	retrospective self-report	15.2

Table 13.6
Intervention and Allocation Characteristics of RCT's of Examining Birthweight

RCT	Study Sites	Implementation of Intervention	Allocation Scheme
Donovan (London)	3 maternity hospitals	Within clinic by clinic staff	Individual randomization
Sexton, Hobel (Maryland)	52 private obs and university clinic	Outside clinic by project staff	Individual randomization
Macarthur, Newton, Knox (Birmingham, UK)	1 maternity hospital	Within clinic by clinic staff	Alternating 4-week accrual

Table 13.7
Quit Rates and Birthweights by Parity for UK and Maryland Cohorts

	Percentage Quit Late Pregnancy, UK*			Birthweight, UK*		
Parity	TX	C	(TX-C)	TX	C	(TX-C)
0	13%	7%	6%	3164	3068	96
> 1	7%	6%	1%	3163	3171	-8
	Percentage Quit Late Pregnancy, MD†			Birthweight, MD†		
Parity	TX	C	(TX-C)	TX	C	(TX-C)
0	36%	10%	26%	3226	3102	124
> 1	31%	6%	25%	3275	3163	112

* *Macarthur, Newton and Knox*

† *Sexton and Hebel: This excludes baseline quitters.*

Table 13.8
Quit Rates and Birthweights for
Blacks and Whites in Maryland Cohort

	Percentage Quit Late Pregnancy*			Birthweight		
Race	TX	C	(TX-C)	TX	C	(TX-C)
Blacks (N = 296)**	39%	6%	33%	3080	2986	94
Whites (N = 439)**	28%	8%	20%	3384	3248	136

* *Eighth month*

** *Excludes baseline quitters*

Table 13.9
Additional Randomized Clinical Trials of Smoking Cessation

Investigations (1st Author, Location, and Total Number)	Program	Quit (Percentage) TX	Control
Baric (United Kingdom); N = 110	Health provider message; materials	14%	4%
Secker-Walker (Vermont); N = 249	Health education; 4 individual counseling sessions; materials	14%	9%
Windsor (Alabama); N = 309 N = 309	Health education (brief) Windsor's self-help guide*	14%	2%

* *A second smoking group using the American Lung Association's "Freedom from Smoking" guide had a 6% quit rate.*

Cervical Cerclage: New Evidence from The Medical Research Council/Royal College of Obstetricians and Gynecologists

ADRIAN GRANT, M.D.

INTRODUCTION

This paper is an update of a review of cervical cerclage prepared for the symposium on preterm birth held at Evian in 1985.[1] Since then, the interim results of the first 905 women participating in the Medical Research Council/Royal College of Obstetricians and Gynecologists (MRC/RCOG) randomized controlled trial have been published.[2] The purpose of this update is to review the interim results of the MRC/RCOG trial in the context of the three smaller trials of cervical cerclage which were discussed in some detail at Evian.[3-5] Full details of the MRC/RCOG trial are available elsewhere,[2] so only the most important features will be described here.

Medical Research Council/Royal College of Obstetricians and Gynecologists Trial

The impetus behind the MRC/RCOG Cervical Cerclage Trial was recognition of the high mortality and morbidity associated with preterm delivery.[1] Cervical cerclage was identified as a strategy for prevention which had been poorly assessed. It was recognized that, in rare cases, the operation may have serious adverse effects, and that there was no sound evidence of its efficacy. Uncertainty about the place of the operation was confirmed in a survey conducted by the MRC/RCOG Working Party on Preterm Labor in 1979 (unpublished observations), which revealed extraordinarily wide variation in the use of the procedure by British consultant obstetricians. This variation was one of the reasons for choosing relatively flexible entry criteria—obstetricians' *uncertainty* as to the advisability of cerclage. There was no possibility of reaching consensus about where the uncertainty lay. Furthermore, it was argued that cases which would meet more rigid entry criteria would be entered into a trial with more open criteria by those obstetricians whose uncertainty happened to coincide with the rigid criteria. The advantage of this strategy was that other types of cases for which other obstetricians were uncertain about the advisability of cerclage would be entered into the trial. Any beneficial effect would be expected to be mediated by prolongation of pregnancy irrespective of indication. Nevertheless, the usefulness of cerclage is likely to depend on the indication. It was therefore hoped that a wide variety of patients would be randomized and that secondary analysis of patients in six prespecified subgroups would then help to determine who (if anyone) could be expected to benefit from cerclage.

In practice, 70 percent of the women who entered the trial had had one or more second trimester miscarriages or preterm deliveries; 10 percent had a history of possible past cervical damage (for example, cone biopsy or cervical amputation); and, in the remaining 20 percent of the cases, cerclage was considered on the basis of other indications, such as previous termination of pregnancy and or previous first trimester miscarriage. The trial groups were well balanced with respect to these various indications. The design of the trial was pragmatic. It was recognized that the clinical situation might change as pregnancy progressed, and the aim was to compare two policies in the form of recommended management at trial entry. In fact, 92 percent of those allocated to cerclage received a suture (of those who did not, 5% did not wish to have a suture and 3% miscarried before the stitch could be inserted), and, of those allocated to the control group, 7 percent had cerclage (5% because the cervix was judged to be opening and 2% because the patient decided after entry that she would like a suture).

Two hundred obstetricians (from 12 countries) have contributed cases to the trial. Although randomization *within* specialty was not performed, cerclage and control cases were evenly distributed for each participating obstetrician. Most cases (95%) were entered before 20 completed weeks' gestation; the latest gestation at entry was 29 weeks. Cases were entered and randomized by telephone. Most obstetricians used the telephone randomization service

provided by the Clinical Trial Service Unit in Oxford, but other randomization centers were established in Italy, Zimbabwe, and Hungary.

Review of the overall results of the four randomized trials

Since the MRC/RCOG trial was established, the three smaller randomized controlled trials comparing cervical cerclage with conservative management have been reported.[3-5] These were discussed at Evian[1] and have been reviewed elsewhere.[6] Only Rush's study[5] of singleton pregnancies with an overall preterm delivery rate of 33 percent shows much similarity to the MRC/RCOG trial. Dor[4] investigated twin pregnancies only; Lazar[3] recruited women with singleton pregnancies with an overall preterm delivery rate of only six percent.

Obstetric management

The results of the MRC/RCOG trial[2] are consistent with those of the previously reported trials (where data are available) in suggesting increased obstetric intervention associated with cerclage as judged by admission to hospital, the use of oral betamimetics, induction of labor, and cesarean section (see table 14.1).

Pregnancy outcome

Where the MRC/RCOG trial[2] does differ from the other trials is in its suggestion of a beneficial effect of cerclage on length of gestation and vital outcome (see table 14.2). The three smaller trials show a tendency toward shorter gestation and higher mortality in the cerclage group. In contrast, there were 5 percent fewer deliveries between 20 and 32 weeks' gestation in the MRC/RCOG trial, which, if real, would be equivalent to the prevention of 1 preterm delivery for every 20 sutures inserted. The result is of only marginal statistical significance, however, and is compatible with a wide range of possible effects of the operation on the occurrence of delivery before 33 weeks. The difference in the timing of delivery in the MRC/RCOG trial was also reflected in improved survival, again contrasting with the smaller trials (see table 14.2).

Cervical cerclage for specific indications

As planned, possible differential effects of cervical cerclage were investigated in secondary analyses of the MRC/RCOG data stratified by possible indications for cerclage, such as past obstetric history of second trimester miscarriage or preterm delivery, or previous surgery to the cervix, or multiple pregnancy.[2] Three of the strata generated in this way are broadly similar to women recruited to the other three trials.

Cervical cerclage after previous second trimester miscarriage and/or preterm delivery

Six hundred and thirty women (70%) in the MRC/RCOG interim analysis had singleton pregnancies and a past history of one or more second trimester miscarriages or preterm deliveries (but no history of surgery to the cervix). These characteristics are similar to the entry criteria of the South African trial.[5] Table 14.3 provides an overview of the outcome in these two subgroups with respect to delivery before 33 weeks

and fetal or neonatal death. As discussed earlier, the South African trial, if anything, suggested a small adverse effect of cerclage, but with wide confidence intervals. In contrast, the stratified analysis of the MRC/RCOG data suggests a large beneficial effect of the operation, with estimates of the odds ratios of 0.67 and 0.66. In fact, this analysis revealed that most of the differences observed in the primary analyses of the MRC/RCOG trial were in women with a past history of second trimester miscarriage or preterm delivery. Furthermore, the more early deliveries in the past, the greater the apparent benefit.[2] The MRC/RCOG trial provides 80 percent of the data in table 14.3; this explains the typical odds ratios of 0.79 and 0.76 with confidence intervals between 0.52 and 1.10. To state these results another way, the estimate is that the insertion of about 18 cervical sutures will prevent 1 delivery before 33 weeks, but this statement cannot be made with any confidence.

Previous surgery to the cervix as an indication for cervical cerclage

Only 96 women in the MRC/RCOG interim analysis had a past history of cone biopsy or cervical amputation, and there are no women with similar histories in the other trials. The odds ratios for the main measures of outcome were all near unity, but because confidence intervals are very wide, these analyses are of little practical use. Far larger numbers are required.

Twin pregnancy as an indication for cervical cerclage

The 50 cases in the Israeli trial[5] were all twin pregnancies, and there were 24 twin pregnancies in the interim analyses of the MRC/RCOG trial. The outcome with respect to delivery before 33 weeks and miscarriage, stillbirth, and neonatal death for these 74 cases is summarized in table 14.4; the data are too sparse to allow any conclusions. In the Dor study,[4] 14 of the 50 fetuses in the cerclage group did not survive the early neonatal period, as opposed to 11 of the 50 in the control group. The timing of these losses was generally similar in the two groups. In the sutured group, three women miscarried in the 14th, 16th, and 17th weeks, while in the nonsutured group, two women miscarried in the 15th and 16th weeks. This demonstrates how difficult it is to make a judgment in individual cases as to whether or not the insertion of a cervical suture actually caused a miscarriage. Three women in each group subsequently delivered prior to 33 completed weeks. The extra miscarriage in the sutured group is largely responsible for the difference in mortality: Thirty-nine (78%) survived the neonatal period in the control group, compared with 36 (72%) in the cerclage group.

Cervical cerclage for other reasons in women at moderate or low risk of early delivery

One hundred and fifty-five women (17%) included in the interim analysis of the MRC/RCOG trial had neither a previous second trimester miscarriage, nor preterm delivery, nor previous surgery to the cervix, nor twin pregnancy. Many had histories of previous first trimester miscarriages. This stratum seems most similar to the French trial, and the outcome of these two groups is summarized in table 14.5. Again, the confidence intervals of the typical odds ratios are wide because the numbers of events are so small.

Evidence from the randomized trials of possible adverse effects of cervical cerclage

A wide variety of possible adverse effects of cervical cerclage (in addition to increased obstetric intervention) were reported in the interim analysis of the MRC/RCOG trial. It was impossible to ascribe many of them to the operation with any confidence. Cervical trauma and difficulties in removing the stitches were each reported in 6 of the 450 women treated with cerclage. Prelabor rupture of the membranes was associated with cervical cerclage in the South African trial,[3] but this difference was not observed in the Israeli trial.[4] Puerperal pyrexia was reported more frequently in the cerclage group of both the MRC/RCOG trial and the South African trial. This is consistent with observational studies and appears to be a real effect of the operation.

Conclusions

The 1,655 cases entered into the four randomized controlled trials included in this review provide a less than adequate basis for clinical decisions about the use of cervical cerclage. Three hundred more cases have been entered into the MRC/RCOG trial; ideally, however, far larger numbers are required, particularly for the important analyses of subgroups.

Unlike most medical treatments, cervical cerclage has the paradoxical potential to both prevent and cause early delivery. The balance between these two effects is likely to depend on the inherent risk of early delivery in the cases treated. Taking this consideration and the other recognized adverse effects of the operation into account, it seems sensible to limit the use of the operation to cases with a high likelihood of benefit. Current evidence suggests that increasing numbers of previous second trimester miscarriages or preterm deliveries constitute the firmest basis for making this decision. There is currently no sound evidence to support the use of cervical cerclage on the basis of previous surgery to the cervix or multiple pregnancy.

Cervical cerclage remains unsatisfactorily evaluated. It is unfortunate that larger numbers of randomized studies have not been conducted. Nevertheless, the trials which have been mounted are beginning to provide good evidence about the balance between the benefits and hazards. They should provide a template for future research into the effectiveness of the procedure.

Acknowledgments

I am very grateful to the Department of Health and Social Security for salary and other support. The MRC/RCOG trial was supported by a Special Project Grant from the Medical Research Council.

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Statistical Findings: Cervical Cerclage: New Evidence From the Medical Research Council/Royal College of Obstetricians and Gynecologists

Table 14.1
Effects of Cervical Cerclage on Obstetric Management—Evidence from the Randomized Trials

	Cerclage	No Cerclage	Odds Ratio	95% Confidence Interval
A. Admission to hospital				
MRC/RCOG interim report (1988)	135/454	114/451	1.25	0.93–1.67
Rush et al. (1984)	30/96	19/98	1.87	0.98–3.57
Lazar et al. (1984)	85/268	41/238	2.17	1.45–3.24
typical odds ratio (95% CI)			1.55	1.24–1.93
B. Use of oral tocolytics				
MRC/RCOG interim report (1988)	113/454	107/451	1.07	0.79–1.44
Rush et al. (1984)	12/96	8/98	1.59	0.63–4.01
Lazar et al. (1984)	127/268	73/238	2.01	1.41–2.87
typical odds ratio (95% CI)			1.40	1.12–1.75
C. Induction of labor				
MRC/RCOG interim report (1988)	85/454	69/451	1.27	0.90–1.80
Rush et al. (1984)	9/96	8/98	1.16	0.43–3.14
Lazar et al. (1984)	49/268	39/238	1.14	0.73–1.81
typical odds ratio (95% CI)			1.22	0.93–1.59
D. Cesarean section				
MRC/RCOG interim report (1988)	68/454	56/451	1.24	0.85–1.81
Rush et al. (1984)	19/96	18/98	1.10	0.54–2.24
Lazar et al. (1984)	33/268	22/238	1.37	0.78–2.40
Dor et al. (1982)	9/25	7/25	1.43	0.44–4.65
typical odds ratio (95% CI)			1.26	0.95–1.66

Table 14.2
Effects of Cervical Cerclage on (A) Delivery Before 33 Weeks and (B) Miscarriage, Stillbirth, and Neonatal Death Combined—Evidence from the Four Randomized Trials

	Cerclage	No Cerclage	Odds Ratio	95% Confidence Interval
A. Delivery before 33 weeks				
MRC/RCOG interim report (1988)	59/454	82/451	0.67	0.47–0.97
Rush et al. (1984)	12/96	10/98	1.26	0.52–3.04
Dor et al. (1982)	6/25	5/25	1.26	0.33–4.73
Lazar et al. (1984)	4/268	1/238	2.99	0.51–17.41
typical odds ratio (95% CI)			0.79	0.58–1.09
B. Miscarriage, stillbirth, and neonatal death				
MRC/RCOG interim report (1988)	37/454	54/451	0.66	0.43–1.01
Rush et al. (1984)	9/96	9/98	1.02	0.39–2.69
Dor et al. (1982)	7/25	6/25	1.23	0.35–4.28
Lazar et al. (1984)	2/268	1/238	1.74	0.18–16.84
typical odds ratio (95% CI)			0.76	0.52–1.10

Table 14.3
Effects of Prophylactic Cervical Cerclage After Previous Second Trimester Miscarriage or Preterm Delivery on (A) Delivery Before 33 Weeks and (B) Miscarriage, Stillbirth, and Neonatal Death

	Cerclage	No Cerclage	Odds Ratio	95% Confidence Interval
A. Delivery before 33 weeks				
MRC/RCOG interim report (1988)	43/325	61/305	0.61	0.40–0.93
Rush et al. (1984)	12/96	10/98	1.26	0.52–3.04
typical odds ratio (95% CI)			0.70	0.48–1.02
B. Miscarriage, stillbirth, and neonatal death				
MRC/RCOG interim report (1988)	25/325	41/305	0.54	0.33–0.90
Rush et al. (1984)	9/87	9/89	1.03	0.39–2.71
typical odds ratio (95% CI)			0.62	0.40–0.98

Table 14.4
Effects of Prophylactic Cervical Cerclage for Twin Pregnancy on (A) Delivery Before 33 Weeks and (B) Miscarriage, Stillbirth, and Neonatal Death

	Cerclage	No Cerclage	Odds Ratio	95% Confidence Interval
A. Delivery before 33 weeks				
MRC/RCOG interim report (1988)	1/10	4/14	0.34	0.05–2.40
Dor et al. (1982)	6/25	5/25	1.26	0.33–4.73
typical odds ratio (95% CI)			0.83	0.28–2.49
B. Miscarriage, stillbirth, and neonatal death				
MRC/RCOG interim report (1988)	1/10	1/14	1.43	0.08–25.35
Dor et al. (1982)	7/25	6/25	1.23	0.35–4.28
typical odds ratio (95% CI)			1.26	0.40–3.96

Table 14.5
Effects of Prophylactic Cervical Cerclage for Women at Moderate or Low Risk of Early Delivery on (A) Delivery Before 33 Weeks and (B) Miscarriage, Stillbirth, and Neonatal Death

	Cerclage	No Cerclage	Odds Ratio	95% Confidence Interval
A. Delivery before 33 weeks				
MRC/RCOG interim report (1988)	6/73	7/82	0.96	0.31–2.98
Lazar et al. (1984)	4/268	1/238	2.99	0.51–17.41
typical odds ratio (95% CI)			1.34	0.52–3.47
B. Miscarriage, stillbirth, and neonatal death				
MRC/RCOG interim report (1988)	3/73	5/82	0.67	0.16–2.77
Lazar et al. (1984)	2/268	1/238	1.74	0.18–16.84
typical odds ratio (95% CI)			0.87	0.26–2.92

Prevention of Intrauterine Growth Retardation with Antiplatelet Therapy

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INTRODUCTION

The treatment of intrauterine growth retardation (with or without associated hypertension) and complications of pregnancy-induced hypertension (e.g., preeclampsia, eclampsia, and abruptio placenta) is most often purely palliative. Delivery of the fetus is usually the only cure, which often results in serious prematurity and neonatal problems.

Numerous studies[1-3] have attempted to analyze the phenomena responsible for these complications. As a result, the following elements have been clarified to date:

1. Preeclampsia is often associated with a disseminated intravascular coagulopathy with a reduction in the platelet count, a consump-

tion of factor VIII, and an augmentation of fibrin degradation products. The microscopic and grossly visible placental thrombotic lesions which are commonly seen are a consequence of these coagulation disturbances.

2. These placental infarcts appear to be associated with the presence of fibrin deposits in the intervillous spaces. In certain cases, sufficient fibrin is accumulated to produce a true retroplacental hematoma. In addition, similar fibrin deposits are commonly found in other organs (e.g., the liver or the brain). These findings encourage us to believe that the coagulation abnormalities observed in preeclampsia are critical to the development of both maternal and fetal complications.

In pregnancy-induced hypertension, an increase in the production of thromboxane A_2 (TXA_2) is often found. This product (the principal metabolite of arachadonic acid in platelets) is a powerful vasoconstrictor and a stimulator of platelet aggregation. The origin of the enhanced production of TXA_2 appears to be at the level of the placenta and the platelets themselves. The increase in TXA_2 without a corresponding increase in the production of prostacyclin leads to a relative predominance of thromboxane A_2 in the uteroplacental circulation. Prostacyclin works in opposition to thromboxane A_2, both in terms of vascular tone and platelet function. This imbalance between thromboxane A_2 and prostacyclin$_2$ is believed to be due to pathological interactions at the platelet-platelet and platelet-vascular level.

Previously, research teams have attempted to treat preeclampsia with heparin. Results have been either disappointing or, at best, transitory. In our opinion, this ineffectiveness may have been due to relative late initiation of therapy.

In one epidemiological study, Crandon[4] reported that women who frequently used aspirin had a decreased incidence of gestational hypertension or, if present, fewer additional complications such as preeclampsia.

By 1978, we had decided to establish a study which examined the effectiveness of the combination of aspirin and dipyrimadole in the prevention of pregnancy-induced hypertensive complications. There were several reasons for this choice. First, aspirin effectively impedes platelet aggregation, probably through inhibition of platelet cyclooxygenase, which then results in blockage of the synthesis of thromboxane A_2. Second, aspirin has been extensively prescribed by cardiologists to reduce thrombotic complications in patients with valvular protheses and following coronary artery surgery. Lastly, aspirin has been used to prevent recurrences of arterial thrombotic problems.

The majority of authors[5–9] have utilized small dosages of aspirin (less than 150 mg per day) in order to preserve the beneficial effects of prostacyclin, the hypothesis being that the synthesis of prostacyclin in the vascular endothelium is less sensitive to aspirin inhibition than that of thromboxane A_2 in platelets.

The second medication, dipyrimadole,[10] has been associated with aspirin in a number of studies; however, it has been difficult to distinguish its specific action from that of aspirin. Through its inhibition of phosphodiesterase, it may potentiate the action of aspirin by retarding the destruction of adenosine monophosphate, thus making platelets more sensitive to prostacyclin. Dipyrimadole may also have an

autonomous action; it may stimulate prostacyclin synthesis in platelets.

These considerations logically support the proposal of aspirin and dipyrimadole as a preventive therapy modality for pregnancy-induced hypertension.

We will first examine a review of the therapeutic trials using aspirin and/or dipyrimadole. Tables include only statistics from published trials; information from brief or oral communications and studies in progress will be included in the discussion.

These studies can be analyzed according to four criteria:

1. What were the criteria for inclusion—intrauterine growth retardation exclusively, or complications of gestational hypertension in general?
2. Was the study prospective?
3. Were the patients randomized?
4. Was there a placebo-control group?

At this time, to our knowledge, five controlled studies exist: The study by our group begun in 1978;[5] the study by Wallenburg published in 1986;[6] the study by Wallenburg published in 1987;[7] and the two multicentric studies currently in progress in France and in Belgium (group Pergar and group Epreda). Table 15.1 summarizes different aspects of these studies. We will next examine the methods and results of the three studies actually completed.

Material and Methods

For each study, we have indicated the criteria for inclusion, treatment regimens, gestational age at onset, number of patients included, and number of pregnancies observed (see table 15.2).

The expression *treatment utilized* means uniquely antiplatelet aggregation therapy. Other more traditional antihypertensive medications are not specified.

Concerning criteria for inclusion, the following should be noted:

1. Study A (see table 15.1) has a heterogeneous recruitment (this is probably one of its principal faults). A certain number of patients are even selected under the heading, "vascular risk."
2. Study B has an original and interesting selection process in that it proposes a method for testing nulliparas. Their criteria for inclusion is an increased sensitivity to an intravenous angiotensin II challenge. A response is considered positive if diastolic blood pressure rises by 20 mm Hg at a dose equal to or less than 10 mg/kg/min.
3. The three final studies used fetal weight related to gestational age at delivery of either one or two preceeding pregnancies as the sole criterion for admission.

Results

The principal criteria evaluated during these studies are shown in table 15.3. The numbers and the mode of expression (i.e., absolute numbers or percentages) are as published. When two numbers are listed, the first corresponds to the control group, and the second to the treatment group.

Discussion

Before beginning the discussion of results, it appears more logical to comment on the criteria of inclusion, certain ethical problems, the optimal dosage, and the possible adverse effects of this therapy.

Criteria for inclusion

The most logical selection process (and the method being used for the two studies in progress) is to use prior IUGR confirmed at delivery as the criterion for inclusion. It is the only one that can be considered objective. The two studies (D and E on table 15.1) include two types of patients classified according to whether there have been one or two prior episodes of IUGR. This stratification attempts to identify future indications for therapy. Perhaps the benefits of therapy will be shown to outweigh the risks when the probability of recurrence is high (i.e., when there have been two preceding pathological pregnancies).

Trial B, using the angiotensin II sensitivity test as its inclusion criterion, resolves only partially the problem of identification in primiparas.

Ethical Considerations

Participation in a study such as this posed numerous ethical questions which were discussed at length by our ethics committee. The principal point of debate was whether or not it was appropriate to propose to women with a history of two prior pathological pregnancies that they attempt a third pregnancy with a possible placebo. Wallenburg chose not to enter his patients into an internal control group because of his implicit belief in the following two arguments: (1) That the efficacy of treatment was beyond any doubt (in our opinion, this position was not sufficiently admissible); and (2) that the treatment was innocuous (in our opinion, this argument was also uncertain). Because we believed that formal proof did not exist for either of these two arguments, we felt that our study was justified.

Optimal Dosage

In our first study, the treatment regimen of 150 mg aspirin per day with 300 mg dipyrimadole per day was used; however, it appeared that even smaller doses might be as effective. Dosages currently being used are between 1 and 2 mg/kg/day for aspirin and 225 mg/day for dipyrimadole. In Wallenburg's study (1987), it was shown that dosages of aspirin as low as 50 mg/day and of dipyrimadole as low as 225 mg/day significantly diminished production of platelet thromboxane A2, which was inferred indirectly through measurements of malondialdehyde. Concentrations of malondialdehyde, a stable byproduct of platelet thromboxane synthesis, were reduced to 5–10 percent of baseline levels. On the other hand, levels of 6-oxoprostaglandin $F_{1\alpha}$, a prostacyclin metabolite, were not significantly decreased. Both of these observations lend further support to the effectiveness of low dose aspirin and dipyrimadole.[4,10,12]

Each of the three completed studies unequivocally demonstrated in its treatment group (whether randomized or in comparison with the controls) the following findings: (1) A reduction in the rate of intrauterine growth retardation, and (2) a reduction in the rate of secondary complications.

The above findings were also indirectly confirmed by other parameters. Placental examination revealed a reduction in placental lesions; and our study (as noted in table 15.4) demonstrated an improvement in plasma volume, plasma uric acid, and platelet count.

In our study, the duration of pregnancy at the time of delivery in the treatment group was increased significantly, whereas in Wallenburg's study (1987), it was one to two weeks shorter in the treatment group than in the control group. This latter difference was not significant. The disparity between the two studies may perhaps be explained by population differences, with an usually high incidence of prior uterine scar and repeat cesarean section in Wallenburg's treatment group when compared with his control group.

In our study (and we believe it will be confirmed by the larger study in progress), the reduction in prematurity is one of the major benefits of treatment.

In all three studies, no hemorrhagic complications were noted in either mother or neonate. In addition, no fetal malformations were observed in any of the treatment groups that could be attributed to the medications. In our study, several patients receiving dipyrimadole complained of headaches. These regressed rapidly with reduction in the dipyrimadole dose. Cessation of treatment was never required.

It seems premature, however, to conclude that the treatment regimen is innocuous.

When considering the potential adverse effects of aspirin, it is important to note that this medication does not generally modify the classical coagulation parameters except for those of platelet aggregation. In practice, bleeding time (as measured by the IVY method, which is the most reproducible) is necessary to evaluate hemostatic changes. In patients receiving low-dose aspirin, significant prolongation of their bleeding time may occasionally be observed. Moreover, after stopping aspirin therapy, a delay of six to eight days is usually required for normalization of platelet function.

Several publications have reported incidences of maternal hemorrhagic complications at the time of delivery and neonatal cutaneous and mucosal lesions in women consuming aspirin.[3] It must be noted, however, that these studies involved considerably higher dosages of aspirin. The same explanation can be made concerning the study by Daffos, in which he reported an umbilical cord puncture associated with a moderately severe fetal coagulation disturbance in a woman taking aspirin.

Cases of premature closure of the ductus arteriosus have been described in women on aspirin therapy (again, dosages were larger than those in our study).

Conclusion

It is our belief that aspirin and dipyrimadole will be shown to be an effective therapy in the prevention of intrauterine growth retardation in women who have had a prior similarly complicated pregnancy, and perhaps even more significantly effective in women with a history of two abnormal pregnancies. This treatment modality appears to be both effective and equally devoid of major risks. A controlled randomized double-blinded study with a placebo group, however, is felt to be

necessary before encouraging utilization of these medications. In addition, the respective roles of aspirin and dipyrimadole need to be clarified. This study is currently in progress.

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Statistical Findings: Prevention of Intrauterine Growth Retardation with Antiplatelet Therapy

Table 15.1
Design Characteristics of Five Reviewed Studies

	A	B	C	D	E
Prospective	+	+	+	+	+
Randomization	+	+	-	+	+
Double-blind	-	+	-	+	+
Placebo control	-	+	-	+	+
Date	1978–1984	*–1986	1983–1986	1985–†	1985–†

* *Start date for study not available* † *Study not completed at the time of this writing.*

Table 15.2
Sample Sizes and Other Criteria of Five Reviewed Studies

	A	B	C	D	E
Criteria for Inclusion	IUGR Acc. HTN HTN ess. Terrain	I Pare Test Angio II	IUGR ≥ 2	IUGR: 1 IUGR ≥ 2	IUGR: 1 IUGR ≥ 2
Treatment					
group 1	Asp. 150 Dip. 300	Asp. 60	Asp. 60 Dip. 225	Dip. 225	Asp. 150 Dip. 225
group 2	0	0	0	Placebo	Asp. 150
group 3	—	—	—	—	Placebo
Gestational Age at onset	16	28	16	16	16
Number of Patients	93	44	48	300*	300*
Number of Pregnancies	93	44	57	300	300

Table 15.3*
Summary of Results of Three Completed Studies

	A		B		C	
	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group
Number of pregnancies	48	45	21	23	30	27
Premature births	12	5	4	0	—	—
Mean gestational age at delivery	36.5	38.6	39	40	38	37
IUGR p 3	7	0	3	0	7	0
IUGR p 10	13	4	6	4	16	4
Hypertension	22	19	4	2	15%	6%
Intrauterine fetal development	3	0	0	1	0	1
IUFN + Neonatal death	5	0	—	—	—	—
Abruptio placenta	3	0	—	—	—	—
Preeclampsia	6	0	7	0	—	—
Eclampsia	0	0	1	0	—	—
Cesarean sections	13	8	7	1	22%	44%
Birthweight	2625	3172	3040	3190	—	—
Normal pregnancies	12	29	—		—	—
Placental weight	509	599	—		—	—

*Where two numbers are listed, the first corresponds to the control group.

Table 15.4
Evolution of Biomechanical Monitors

	Treatment Group (N=48)	Control Group (N=45)	*p*
Baseline:			
Plasma uric acid (umol/1)	221 + 62	220 + 52	NS
Platelet Count (x1.000/ml)	245 + 57	233 + 59	NS
Week Prior to Delivery			
Plasma Uric Acid	270 + 69	293 + 83	NS
Platelet Count	249 + 66	209 + 57	< 0.02
Plasma Volume	56 + 7.5	49 + 8.1	< 0.02

Does Calcium Supplementation Reduce Pregnancy-Induced Hypertension and Prematurity?

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J.T. Repke, M.D.

Introduction

Pregnancy represents a period of very high calcium demand. There is an increased fetal requirement resulting in a total calcium accumulation at term of approximately 30 g, 30 percent of which is deposited during the third trimester. Some of the maternal adaptive mechanisms that could compensate for such high fetal demands are partially inhibited during pregnancy.[1] Furthermore, pregnancy has been suggested to be a period of "obligatory" high urinary calcium output,[2] while maternal bone calcium is protected.[3] Finally, although intestinal absorption of calcium can increase,[4] this is associated with an increased parathyroid hormone secretion during pregnancy.

It is possible, therefore, that when pregnant women are put in a nutritional situation that can alter this metabolic balance, they can be at higher risk for pathological events that have calcium-dependent mechanisms. This could affect smooth muscle contractility of the vascular system and uterus. Several epidemiological studies in pregnant and in normotensive and hypertensive subjects consistently showed an inverse relationship between calcium intake and blood pressure.[5,6,7]

Randomized controlled clinical trials of calcium supplementation in normotensive women, men, and mildly hypertensive patients have demonstrated a significant reduction in blood pressure.[5] Data from two randomized clinical trials show a significant reduction in blood pressure in the calcium-supplemented group at term (see figure 16.1). Furthermore, a dose-effect relationship is observed when our two studies are combined (see figure 16.2). The effect is maximized with a daily dose of 2.0 g of calcium and is less with 1.0 g of calcium supplementation.

Based on this information, we developed the hypothesis that calcium supplementation during pregnancy can decrease the incidence of pregnancy-induced hypertension (PIH)/preeclampsia and preterm delivery when compared with the placebo group. The effect could be mediated by reducing smooth muscle tension (e.g., vascular and uterine).

Background Information: the Relationship between Calcium Supplementation and PIH/Preeclampsia

Table 16.1 presents summary data from four studies that provided information on the effect of calcium supplementation on PIH/preeclampsia rates. Three randomized placebo controlled clinical trials and one uncontrolled matched study were conducted. In one of our clinical trials, which was not designed to evaluate the incidence of PIH, the placebo group had a relative risk of 2.8 of developing PIH as compared with the calcium group (11.1% v. 4.0%).[5] A preliminary report from a randomized clinical trial conducted in Ecuador demonstrated that the group receiving 2.0 g of calcium a day (N = 46) had an incidence of PIH of 6.5 percent, as compared with a placebo group (N = 46) which had an incidence of 28.2 percent ($p < 0.01$).[9] Finally, a randomized controlled clinical trial was conducted in India in a population with a dietary calcium intake of 500 mg/day. The study population was randomly assigned to a dietary intake of 375 mg/day of elemental calcium and 1200 IU of vitamin D/day or to a placebo group. A non-statistically significant reduction in the incidence of preeclampsia (> 140/90 mm Hg and urinary proteins > 300 mg/24 hrs) (6%) was observed in the calcium-supplemented group (N = 188) as compared with the placebo group (9%) (N = 182). It should be remembered that, to detect a difference of this magnitude with a α = 0.05 and a power between 76 and 84 percent, it would have been necessary to study at least 800 patients in each group. When results from the three randomized controlled trials were pooled using the Mantel and Haenszel method,[10,12] women receiving calcium supplementation had a statistically significant reduced risk for pregnancy-induced hypertension, pooled or typical OR = 0.41 (95% CI 0.39–0.78), as compared with the placebo group.

Preliminary Evidence of the Effect of Calcium Supplementation on Pregnancy-Induced Hypertension/Preeclampsia

We will present here preliminary results of a double-blind, randomized, controlled clinical trial of the effect of 2.0 g of elemental calcium (calcium carbonate) a day or a placebo that is being conducted in two different populations. A white lower middle class population was studied at the Centro Rosarino de Estudios Perinatales, Rosario, Argentina. All patients were nulliparous and clinically healthy. At the time of this presentation, 426 patients had been enrolled and delivered their infants. The second population was obtained from the Adolescent Pregnancy Clinic of the Johns Hopkins Hospital, Baltimore, Maryland. By March 1988, 177 patients had been enrolled and delivered. All patients were less than 17 years of age at the time of recruitment. Most of the subjects were nulliparous with a known last menstrual period (LMP) and had singleton pregnancies. All were free of any underlying medical disorders, as determined by history, physical examination, and laboratory tests.

Participants in both centers were randomly assigned in a double-blind fashion before 26 weeks' gestation to one of the two treatment groups using a randomization schedule prepared in advance for each population. Among white women, 230 were assigned to the calcium-supplemented group and 196 to the placebo group. Among black women, 85 were assigned to the calcium-supplemented group and 89 to the placebo group. Prenatal care was carried out according to the protocols of each participant's hospital. The study protocol was approved by the Johns Hopkins Hospital's Joint Committee on Clinical Investigation.

Figure 16.3 summarizes the study design, criteria for patient eligibility, and follow-up requirements. The calcium-supplemented groups received four tablets of calcium carbonate per day. Each of these tablets provides 500 mg of elemental calcium, for a total of 2.0 g/day. The placebo group received four tablets of the same weight, size, color, and organoleptic characteristics as the calcium tablets.

Both centers implemented a very elaborate mechanism of monitoring tablet intake and compliance as well as data quality control. Treatment compliance evaluation included questioning patients on pill intake, pill counting at every visit (percentage of pills taken/expected number of pills in that period), changing bottles at fixed times, and counting remaining tablets and urinary excretion of calcium in a random sample of patients.

Blood pressure, one of the main outcomes, was obtained by trained personnel working exclusively for the study; continuous monitoring and quality control mechanisms were implemented. All blood pressures were obtained using random zero sphygmomanometers. Table 16.2 presents reliability evaluation of blood pressure measurements in the three participant hospitals of the Argentina center. It shows high agreement values between the field director and the study nurses. Table 16.3 presents, as an example, evidence of high reproducibility of the blood pressure measure during pregnancy at the Hopkins center, as well as a low zero terminal digit preference for the project coordinator.

Table 16.4 summarizes the primary out-

come variables and the definitions used in this study. Blood pressure values, used independently or with proteinuria obtained by the study nurses or project coordinator, and the diagnosis of PIH and/or preeclampsia made by obstetricians in charge of the clinical care of the patients, but unrelated with the study, were used as one of the primary outcomes.

Gestational age, obtained by using the best obstetric estimation, which includes any ultrasound measure, LMP, uterine height, and the time of the first fetal movements detected, was used to calculate the incidence of prematurity (< 37 weeks).

In the Argentinean (white) population, women enrolled in the calcium-supplemented group took 87 percent of the total expected number of tablets, similar to 86 percent in the placebo group. In the Hopkins population, although compliance figures were lower, they were very similar between the calcium-supplemented and placebo groups (66% v. 64%, respectively). The calcium-supplemented and placebo groups were very similar in most of the sociodemographic and baseline characteristics for the black and white populations. There were, however, differences in maternal weight at randomization, with white patients in the calcium-supplemented group and black women in the placebo group statistically significantly heavier.

Table 16.5 presents the effect of calcium supplementation on the incidence of PIH/preeclampsia. The calcium-supplemented groups had a lower incidence of PIH, as well as a lower incidence of preeclampsia in the white population and lower incidence of proteinuria in the black population (NS). The rates observed in the calcium groups were almost half the values obtained in the placebo groups. The rates of preeclampsia were not presented for the black population because the independent clinical diagnoses were not available at the time of this presentation. At term, however, the placebo group had higher mean systolic blood pressure 115 (+ 9.9) mm Hg, as compared with the calcium group 109.4 (+ 11.2) mm Hg ($p < 0.01$), and higher diastolic blood pressure 74.2 (+ 6.5) mm Hg versus 68.7 (+ 9.1) mm Hg ($p < 0.01$) than the calcium group.

Table 16.6 presents the incidence of prematurity (< 37 weeks) and LBW (< 2500 g) by treatment for the two studied populations. The calcium-supplemented groups had a lower incidence of preterm deliveries, 5.4 percent for whites and 7.1 percent for blacks, than the placebo groups, 9.9 percent for whites and 19.1 percent for blacks. The incidence of LBW was also lower in the calcium group; however, among whites, the magnitude is smaller. Among blacks, those supplemented had an incidence of low birthweight of 10.3 percent, compared with 20.0 percent in the placebo group ($p = 0.07$).

Discussion

We have presented preliminary information on the effect of calcium supplementation on gestational age, blood pressure, and PIH/preeclampsia. In agreement with previous reports (see table 16.1), there is a systematic reduction in blood pressure values and new evidence of reduction in prematurity in the calcium-supplemented groups. There is also pre-

liminary evidence from the white population that calcium supplementation can prevent the development of preeclampsia. Nevertheless, caution should be exercised in interpreting these results. They are obtained from two trials in progress, and some of the results could be modified when all of the patients are recruited and analyzed. It is unlikely, however, that the observed direction of the effect will change dramatically. There remains a need to further elucidate the mechanism whereby calcium supplementation exerts its effect. Previous reports have suggested possible effects on parathyroid hormone,[5] plasma renin activity,[11] and serum magnesium.[15]

Increases in parathyroid hormone (PTH) have been shown to increase intracellular calcium in several cell types. The presumed mechanism is an increase in membrane permeability with subsequent facilitated movement of calcium via slow channels from the extracellular to the intracellular compartments. The question remaining is what effect long-term calcium supplementation will have on PTH, and whether chronic suppression of PTH will in fact result in lower levels of intracellular calcium.

We have previously reported that, in pregnant individuals with initial low levels of plasma renin activity (PRA), calcium supplementation resulted in a greater reduction in blood pressure than in women with higher initial PRA.[11] The uterine vascular bed, being sensitive to angiotensin II, may be affected by calcium-induced changes in plasma renin activity.

Patients with renin-dependent hypertension frequently have depletion of magnesium. Our previous report[17] has also demonstrated increased serum magnesium levels among those pregnant women receiving calcium supplementation. The role of magnesium in hypertension has been well established.[18] Its role as an efficacious tocolytic has also been well established.[19] There is a consistency in these observations. The interaction of calcium, parathyroid hormone, plasma renin activity, and magnesium results in alterations of intracellular calcium. The reduction of intracellular calcium will result in myocyte relaxation. There is no reason to believe that this effect is limited to the vasculature. A similar effect should be expected in the myometrium, with resultant relaxation of the uterine smooth muscle. This alteration of intracellular calcium (i.e., reduction) is presumably the final common pathway in the action of betamimetics, magnesium sulfate, prostaglandin synthesis inhibitors, and calcium channel blockers. Thus, it is not inconsistent to expect that calcium supplementation could have an effect not only on blood pressure but on uterine activity, and therefore on gestational age, and, ultimately, birthweight. While the results presented here are clearly preliminary, we suggest that they are provocative and encouraging. Further research at the clinical and basic science levels will be needed to better characterize the role of calcium in human reproduction.

ACKNOWLEGMENT

Partially supported by grants from the National Dairy Board, the National Dairy Council, and the International Development Research Center (IDRC), Ottawa, Ontario, CANADA.

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Statistical Findings: Does Calcium Supplementation Reduce Pregnancy-Induced Hypertension and Prematurity?

Table 16.1
Incidence of Pregnancy-Induced Hypertension (PIH) Data From Calcium Supplementation Studies

Study	Elemental Calcium Supplement (mg/day)	Total Calcium Intake (mg/day)	Blood Pressure (mm Hg)	PIH incidence (Percentage) Calcium	Placebo	
Kawasaki, N. et al.†	156	942	No effect	4.5 (22)	21.2 (66)	$p < 0.10$
Villar et al.§	1500	900	4–5	4.0 (24)	11.1 (25)	NS
Marya R. et al.‖	375 + 1,200 UI Vit D	500	4–7	6.0 (188)	9.0* (182)	NS
Lopez Jaramillo P.†	2,000	300	—	6.5	28.2	$p < 0.01$

* *Non-Randomized—No Placebo*

† Source: Kawasaki N., Matsui K., Ito M. et al. (1985). Effect of calcium supplementation on the vascular sensitivity to angiotension II in pregnant women. *American Journal of Obstetrics and Gynecology*, 153, 576–582.

§ Source: Villar J., Repke J., and Belizan J. M. (1987). Calcium supplementation reduces blood pressure during pregnancy: Results from a randomized controlled clinical trial. *Obstetrics and Gynecology*, 70, 317–322.

‖ Source: Marya R. K., Rathee S. and Manrow M. (1987). Effect of calcium and vitamin D supplementation on toxemia of pregnancy. *Gynecologic and Obstetric Investigation*, 24, 38–42.

† Source: Lopez-Jaramillo P., Narvaez M., Weigel R.H., and Yepez R. (1989). Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population. British Journal of Obstetrics and Gynecology, 19, 648–655.

Preeclampsia (> 140/90 mm Hg and urinary proteins > 300 mg/24 hours)

Table 16.2
Reliability of Blood Pressure Measurements
Rosario, Argentina (Whites)

	N	Systolic	Diastolic
Hospital A	58	0.82*	0.81
B	28	0.77	0.50
C	54	0.74	0.81

* *Correlation coefficients between field director and study nurses*

Table 16.3
Reliability of Blood Pressure Measurements
Johns Hopkins Hospital (Blacks)

A. Correlation coefficients between blood pressure values by gestational age for project coordinator

Weeks of Gestation	Systolic	Diastolic
28 v. 30	0.76	0.63
32 v. 34	0.61	0.51
36 v. 38	0.81	0.71
38 v. 41	0.66	0.65

B. Zero terminal digit preference (N = 1,011 measures)

Systolic	14.1 (%)
Diastolic	13.1 (%)

Table 16.4
Outcome Variables for the Randomized Clinical Trial of Calcium Supplementation During Pregnancy

Blood Pressure (mm Hg)
(study nurses and project coordinator)

- Random zero sphygmomanometer (diastolic B.P. 4th and 5th found)
- Seated position (Hopkins)
- Supine and lateral (Argentina)

Proteinuria: 300 mg/l proteinuria two times more than 6 hours apart

- (Argentina)
- > 300 mg/l or (+) (Johns Hopkins)

Clinical diagnosis of PIH or Preeclampsia made by obstetricians not related to the study

Gestational age (weeks)

- Best OB estimation (ultrasound, LMP, uterine height, fetal movements)
- Physical examination newborn

Birthweight (grams)

Table 16.5
Effect of Calcium Supplementation on PIH/Preeclampsia: A Randomized Double-Blind Controlled Clinical Trial

	Whites		Blacks
		Preeclampsia	
	BP* > 140 mm Hg and/or Proteinuria	BP* and > 300 mg/l Proteinuria	> 300 mg/l Proteinuria
Calcium (2.0 g/day)	11.7 (230)	1.7 (230)	5.9 (68) (NS)
Placebo	19.4 (196)	3.6 (196)	11.4 (70)

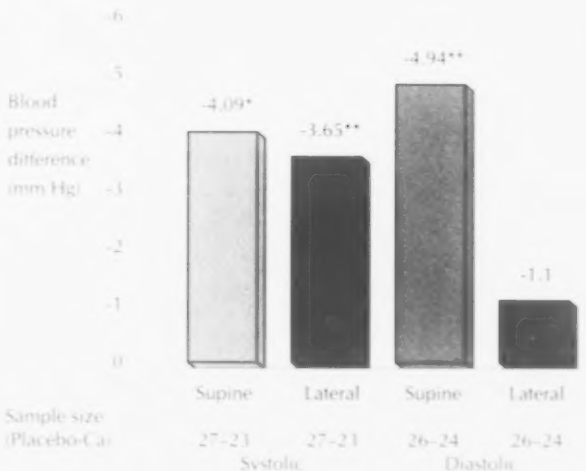
Treatment started between 20 and 26 weeks' gestation
* *2 times > 6 hours*
> 300 mg/l = (+)

Table 16.6
Effect of Calcium Supplementation on the Incidence of Prematurity and Low Birthweight

	Preterm (< 37 weeks) (Percentage)	LBW (< 2,500 g) (Percentage)
Whites		
Calcium	5.4 (223)	8.9 (223)
Placebo	9.9 (192)	10.4 (192)
Blacks		
Calcium	7.1 (85)	10.3 (86)
Placebo	19.1 (89)	20.0 (89)
	$p = 0.01$	$p = 0.07$

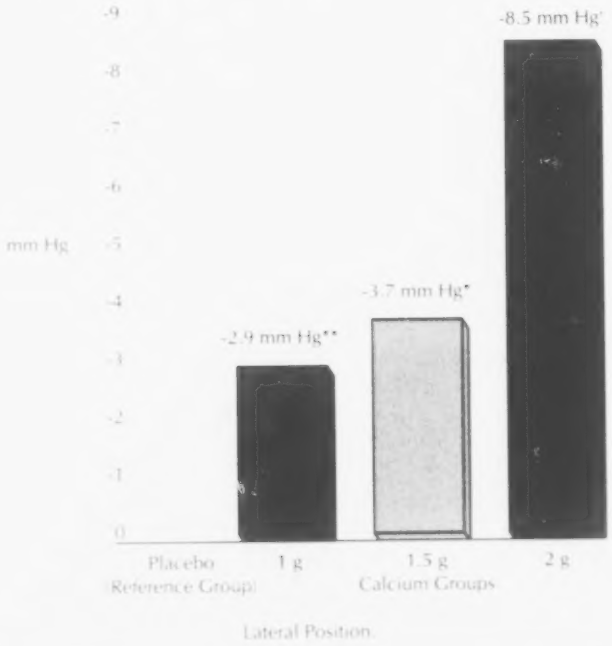
Gestational age: Best obstetric estimation: LMP, Ultrasound, fundal height, and early fetal movement

Figure 16.1
Differences in Adjusted Blood Pressure Mean Values at Term Between Calcium and Placebo Groups (Adjusted for Race and Initial Blood Pressure ≤ 26 Weeks)



*Between groups: $p = 0.06$
**Between slopes (3 last measures): $p < 0.05$

Figure 16.2
Differences in Systolic Blood Pressure at Term Between Calcium-Supplemented and the Corresponding Placebo Groups in Two Studies of Calcium Supplementation During Pregnancy



*Source: Author. (See chapter 16).

**Source: Marya R. K., Rathee S. and Manrow M. (1987). Effect of calcium and vitamin D supplementation on toxemia of pregnancy. *Gynecologic and Obstetric Investigation*, 24: 38–42.

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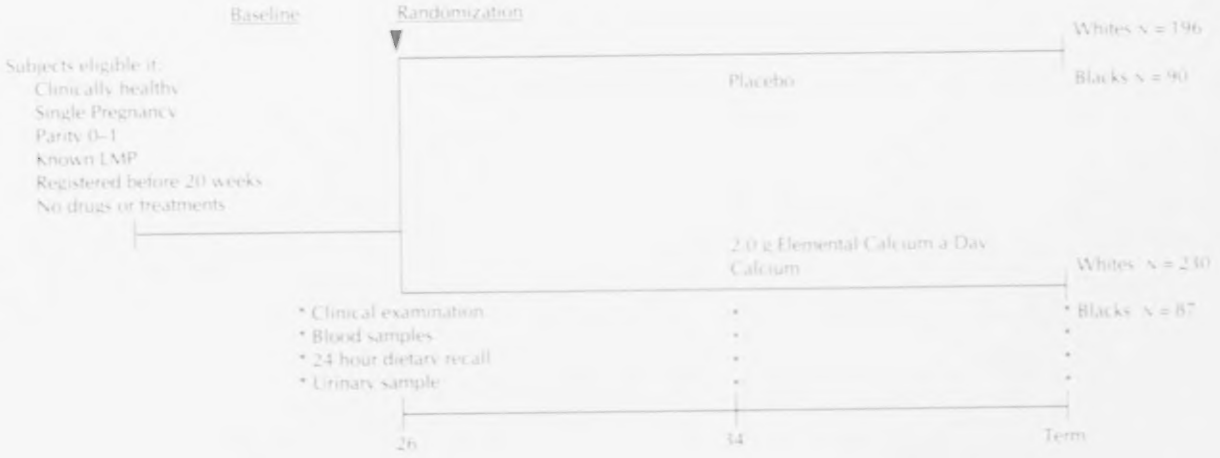
Figure 16.3
Study Design
Randomized Double-Blind Controlled Clinical Trial



Magnesium Supplementation in Pregnancy: A Double-Blind Study

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INTRODUCTION

The recent interest in the element magnesium is probably in part accident and in part due to the development of new techniques, such as atomic absorption spectrophotometry permitting accurate assays. These technological advances facilitate correlation of laboratory results with clinical disorders.

First some important qualities of magnesium are identified. After potassium, magnesium is the second most abundant intracellular cation. On the one hand, its biological effect can be attributed to the formation of chelation compounds. On the other hand, it is a cofactor of ATP (adenosine triphosphate), thus explaining its influence on about 300 enzymatic reactions, such as carbohydrate metabolism, lipid metabolism, and nucleic acid metabolism. It is

involved in stages of protein synthesis and is an important prerequisite for the proper functioning of energy-releasing reactions, such as glycolysis and oxidative phosphorylation.[2]

A person needs 0.16–0.21 mmol of magnesium per kilo of bodyweight per day, which corresponds to 11.5–14.4 mmol per day for a bodyweight of 70 kg. During growth and pregnancy, an additional 4 mmol per day are needed. Based on metabolic studies of pregnant women, the World Health Organization (WHO) Food and Nutrition Boards recommend a supply of 18.5 mmol of magnesium per day during pregnancy (1 mol Mg = 24.3 g Mg).[3]

Investigations during recent years have repeatedly shown that the magnesium content of plasma falls significantly during pregnancy, particularly at the beginning.[4] It is discussed as a physiologic dilution. It should be mentioned that renal magnesium loss in pregnancy increases by 26 percent, shown by 24 urine samples in healthy women during the whole pregnancy.[5]

Chronic hypomagnesemia in the pregnant woman carries over to the tissues. Using myometrium samples of over 100 cesarean sections, it could be documented that the magnesium content of the smooth uterine muscles decreases significantly with increasing pregnancy age. There is also a highly significant correlation between the muscle magnesium content and plasma level.[6]

This leads to the conclusion that, although magnesium intake is not increased during the period of greater need, there is yet more loss through the kidneys due to the increased glomerular filtration, which is not or is inadequately compensated for, and that this long-term hypomagnesemia shows up in growing tissue.

The possibility that magnesium deficiency might cause early delivery was first contemplated following the accidental observation that the reduction of premature labor was improved by treating calf muscle cramps with magnesium. In a subsequent study, 10–15 mmol of magnesium per day were given orally where the dosage of beta-adrenergic drugs could not be reduced. Subjective and objective methods of assessment showed decreased incidence of uterine contractions, and, at the same time, indicated that the required beta-adrenergic dose could be reduced.[7]

The publication of this pilot study caused a number of other studies. In a retrospective study, lower incidences of intrauterine growth retardation, preterm rupture of the membranes, and preeclampsia by magnesium supplementation during pregnancy were described.[8]

Because of the studies cited above, a double-blind study was conducted to clarify whether or not magnesium supplementation has any influence on the pregnant woman and the fetus or the newborn, respectively.

Double-Blind Study

A total of 568 women (normal and high-risk) who attended the outpatient clinic at the Department of Obstetrics, University of Zurich, agreed to participate in the study. They were enrolled in the study as early as possible, but not later than 16 weeks of gestation. The sample size was determined by the limitation of the recruitment period, which, for practical reasons, could not exceed two years.

The method of allocation was based on the subjects' even or odd date of birth. According to their group assignment, the subjects were given either 15 mmol of magnesium-aspartate-hydrochloride (Magnesiocard, Verla Pharmacy, Tutzing, FRG) or 13.5 mmol of aspartic acid per day. At each visit, patients were questioned on regular intake, number of tablets, and side-effects of the medication. A subsidiary analysis was based on 437 women who claimed that they had regularly ingested the magnesium or placebo.

The Mann-Whitney U test was used to compare the central trends. Categorical variables were analyzed using the chi-squared test. The results were considered significant at the 5 percent level. Assessment always used two-tailed tests. Values were given as medians and the 5th and 95th centile. For various reasons, such as refusal to take further tablets, delivery in other hospitals, or abortion, some data were not available for analysis.

Two hundred seventy-eight women were treated with magnesium, and 290 received the placebo. Age, parity, and gravidity were the same in both groups. There was no difference with regard to the birthweight of children born before the start of this study or the duration of previous pregnancies. Based on the clinical history of the patients, the risk of abnormal pregnancy was comparable in the two groups.

The frequency of complaints attributed to the tablets was low and comparable in the two groups. In the magnesium group, 1 woman complained of diarrhea, 4 of nausea, 6 of vomiting, and 6 of heartburn; in the placebo group, 2 complained of diarrhea, 1 of nausea, 10 of vomiting, 6 of heartburn, and 1 of fullness. Median maternal weight increase was 11 kg in both groups, and there was no difference regarding the systolic and diastolic blood pressure and different degrees of oedema. Magnesium serum levels showed no differences between the groups.

Patients were hospitalized if they experienced antepartum hemorrhage, irregular preterm contractions, or progressive cervix maturation. In the magnesium group, 44 women were hospitalized for 533 days. In the placebo group, 65 women had to stay in hospital for 887 days. The average duration of each admission to hospital was the same in both groups. Among indications for admission to hospital, hemorrhage during pregnancy, incompetent cervix, and preterm labor were significantly more frequent in placebo-treated women. There was also no difference in the number of miscarriages.

The median gestation was significantly longer in women treated with magnesium, although the difference between the medians was not more than one day. Delivery before 37 weeks occurred less in the magnesium group, but the difference was not significant. The serum analysis showed that low magnesium levels in the first half of pregnancy are of no predictable value for preterm birth. There were no differences regarding the duration of the first and second stages of labor. The same is true for the incidence of surgery or other complications during delivery.

There are no statistically significant differences between the unselected groups with respect to placental and infant weight; length and head circumference; and birthweight below 2500 g, below 1500 g, and below the 10th per-

centile; however, fewer infants with a head circumference less than 33 cm were found in the magnesium group. There are also no statistically significant differences in arterial and venous umbilical pH or frequencies of infants with an APGAR score of 7 or less. Significantly fewer infants in the group receiving magnesium were admitted to the neonatal intensive care unit. The biggest differences were found in the admission rates for preterm birth and asphyxia. The numbers of the subgroups are too small to show any statistical difference.

In the subsidiary analysis, we excluded those women who did not fulfill the protocol of medication as prescribed, leaving 217 women in the magnesium group and 220 in the placebo group. As expected, the effect of magnesium supplementation demonstrated itself more clearly (see table 17.1). Some of the results that only reflected a trend in the main study became statistically significant, while other results that were already significant in the main study were confirmed at a higher level of significance.

The difference between hospitalization frequencies was significant at a higher level. The number of infants below 2500 g and below 500 g was also significantly smaller in the group of mothers who regularly took magnesium. The difference between numbers of children with a head circumference below 33 cm became highly significant.

A general trend toward improved fetal outcome and adaptation, already seen in the main study, was confirmed by statistically significant results; birthweight, length, and head circumference were higher, and the number of children with a 10-minute APGAR score of 7 or below was less in the group with regular magnesium

Table 17.1
Comparison Between
Magnesium and Placebo Groups

Variable	Magnesium group (N = 278) 50th centile	Placebo group (N = 290) 50th centile	Significance
Indication for Hospitlization			
Hemorrhage (N)	4	17	< 0.05
Incompetent cervix (N)	8	17	< 0.05
Preterm labor (N)	12	26	< 0.05
Gestational age at delivery (weeks/days)	40/0	39/6	< 0.05
Admission to neonatal intensive care unit (N)	20	36	< 0.01

Table 17.2
Comparison Between Magnesium and Placebo Groups
After Exclusion of Patients Who Did Not Take Their
Tablets Regularly

Variable	Magnesium group (N = 217) 50th centile	Placebo group (N = 230) 50th centile	Significance
Birthweight (g)	3340	3300	< 0.05
No. < 2500 g	6	18	< 0.05
No. < 1500 g	0	6	< 0.05
Infant length (cm)	50	49	< 0.05
Head circumference (cm)	35	34	< 0.05
No. with 10-min Apgar score ≤ 7	0	5	< 0.05
No. of women hospitalized	26	48	< 0.01

supplementation. Fewer mothers with mild edema were counted in the magnesium group.

The advantageous effect of magnesium supplementation during pregnancy is clearly documented in decreased incidences of hemorrhages, incompetent cervix, and preterm labor, and in prolonged gestation. If preterm delivery is defined as birthweight below 2500 g, in this study, we could reduce the incidence from 7.7 to 2.8 percent. A statistical difference between the frequencies of abortion could not be seen; however, a positive effect of magnesium supplementation during pregnancy in respect to its clinical syndrome was evidenced by the low incidence of hemorrhage. It is interesting to note that the two infants who were very light for gestational length were seen in the placebo group. One infant born at 31 weeks' gestation weighed 1000 g and another one born at 32 weeks weighed 1190 g. Of course, this number is still too small to establish a significant influence of magnesium supplementation on intrauterine growth retardation.[7]

Conclusion

Magnesium supplementation during pregnancy was associated with significantly fewer maternal hospitalizations, a reduction in preterm deliveries, and less frequent referral of newborns to the neonatal intensive care unit. The results suggest that magnesium supplementation during pregnancy has a significant influence on fetal and maternal morbidity both before and after delivery. The results of this study strongly recommend magnesium supplementation during the whole period of pregnancy.

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An Overview of Trials of Social Support During Pregnancy

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INTRODUCTION

The main purpose of this chapter is to update our earlier review in Evian of controlled trials of social support in pregnancy.[1] We begin, therefore, by summarizing the focus, methods, and conclusions of that review. We then point out the ways in which we have altered these methods for our present work, show the updated results, and discuss their implications for current practice and future research.

1986 REVIEW

We started from the presumption that a pregnant woman is more than just the carrier of her unborn child. She is a person in her own

right, with a life apart from that seen by most antenatal caregivers. This life includes a number of stresses and strains. Pregnancy, although often a joyful experience, may also add to these existing pressures, and may create new stresses. Studies of the relationship between social class, stress, and reproduction suggest that social support in pregnancy may be able to mitigate maternal stress and improve maternal and infant health.[2] We therefore examined the controlled trials of social support in pregnancy.

Methods

Selection of trials

In order to find these trials, we searched the Oxford Database of Perinatal Trials for published[3] and unpublished[4] reports. The criteria for entry in the computerized data base are that the trial participants should be human; that the time of intervention should be during pregnancy or the neonatal period; and that allocation to the intervention should be random or quasi-random (i.e., using alternate allocation or using date of birth or casenote numbers).

For the Evian review, we selected all trials on the data base coded as "counseling, support, and education in pregnancy." Trials included in the analysis were either those designed explicitly to provide social support or those utilizing what we judged to be supportive approaches to antenatal care. These included such disparate interventions as antismoking advice; health education; organization of maternity care; income support; and preparation for pregnancy, childbirth, and parenthood. In the 29 trials of social support in pregnancy so identified we considered seven pregnancy outcomes: Low birthweight, preterm delivery, anaesthesia, analgesia, prolonged labor, instrumental delivery, and adverse psychosocial outcomes.

Statistical methods

We followed the methods of Yusuf and his colleagues[5] to formally combine information from these trials in a procedure which has become known as *meta-analysis* or *overview*.

For each trial, we calculated an odds ratio, which is the odds of getting a particular (usually adverse) outcome (e.g., low birthweight) in the experimental group, compared to or divided by the odds of getting the same outcome in the control group. If the odds ratio is 1, it implies that the odds are the same in the experimental and the control group (i.e., for that outcome, it makes no difference whether the intervention is experimental or control). If the odds ratio is less than 1, it suggests that the experimental intervention offers some protection against this adverse outcome. If the odds ratio is greater than 1, it suggests that the experimental intervention may do harm. The odds ratio is an estimate, and so the confidence with which it can be stated varies directly with the size of the study; that is, the smaller the study, the less confident one can be that the estimate is a true reflection of reality, and the wider the confidence interval is that can be placed around the estimate. Conversely, a large sample size means greater precision and a smaller confidence interval (i.e., the estimate is a more precise reflection of the truth). Therefore, for each study, we show an estimate of the odds ratio with its 95 percent confidence interval. In an overview of several trials, we use

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all of these within-trial estimates to calculate a typical odds ratio, but because several trials are included, we thereby increase the precision of the estimate—that is, we can narrow the confidence intervals.

Conclusions

Our conclusions in 1986 were that "In terms of the seven outcomes considered, the available experimental evidence shows these effects (of the social interventions) to be either inconclusive or beneficial,"[1] and this is supported by the conclusions of the observational studies.[2] We ended our review by calling for better designed, larger trials, specifically in the field of social support.

Present Overview

The aims of our present overview—to review the experimental evidence of the effects of social support in pregnancy—are largely the same as they were three years ago. In this update, however, we adopt four slightly different approaches.

First, this chapter focuses on the two pregnancy outcomes most relevant to the title of the conference: Gestational age at delivery, and birthweight. A number of other outcomes (such as intrapartum events, the health of the mother and baby, health-related behavior, the attitudes and feelings of the mother, and the baby's development) will be considered and discussed elsewhere.[3]

Secondly, our earlier review was based on all trials on the data base with interventions coded as "counseling, support, and education in pregnancy." What this disparate group had in common was that we thought they were the type of intervention that might be supportive. As a response to comments received following this 1986 review, we have limited our inclusions in the present chapter to those in which social support was an explicit aim of the trial (i.e., the authors' intent, rather than our surmise).

Thirdly, the overviews are presented in order of their methodological quality. This quality is assessed in terms of the likely existence of three types of bias: Selection bias at entry, selection bias after entry, and measurement bias. The "best" trials are put first, and the "worst" are put last.

The final methodological difference between the Evian review and the present review arises because, in the interim, a number of trials primarily concerned with social support have been mounted. Thus, we have been able to subdivide our analyses into those based on trials in which social support is the primary intervention, and those trials in which it is an explicit co-intervention. We have looked for a dose effect, expecting that the benefits of support would be greater in the former group.

Characteristics of Trials of Explicit Social Support in Pregnancy

We identified 35 trials of social support in pregnancy. The characteristics of these trials are described in table 18.1. The final column of this table provides examples of the form of words which helped us to decide on their inclusion.

The results of some of the trials have not yet been published[9-12] and still must be considered provisional.

We have categorized the studies under six main headings. The provision of social support is the primary aim in six studies.[13-18] The remaining 29 trials all aim to provide explicit social support, but as a co-intervention. In these trials, the other primary interventions are antismoking advice (3);[19-21] income support (1);[22] information feedback and information sharing (6);[23-28] the organization of care (7);[29-35] and preparation for pregnancy, childbirth, and parenthood (12).[36-53] This last group includes such diverse interventions as, for example, preparation for breastfeeding, nutritional advice, and enhancement of maternal attachment processes. The headings are not necessarily mutually exclusive, and some studies could be categorized under more than one heading.

The entry criteria for the trials included in our overview vary greatly. To a large extent, this reflects the differing aims of the studies. For instance, those studies aimed at reducing the number of cigarettes smoked were targeted at women who were smokers (e.g., [19]). Some studies wishing to alter the organization of care toward more midwifery control concentrated on women at low risk of poor obstetric outcomes (e.g., [39]). In others, midwifery care is compared to medical care for women at high risk (e.g., [10]). In fact, because the principal entry criterion for the study by Kehrer and Wolin[29] was residence in a low-income neighborhood, the studies do not even share in common the entry criterion of being a pregnant woman!

Allocation to the intervention is clearly quasi-random (e.g., using casenote numbers) in five studies.[9,20,30,43,46] Allocation is said to be random in the remaining 30, but often the details are sketchy, or suggest that the author may be using the word *random* in a nontechnical sense.

The sample sizes are equally variable, ranging from 10 women[47] to 1,763 pregnant women.[40] In two papers[51,52] the sample size is not given. Overall, the studies are based on at least 5,500 women allocated to a supportive intervention in pregnancy, and at least 5,600 women with less support serving as controls.

As with the entry criteria, the outcomes under investigation largely reflect the type of intervention being offered. Some include such traditionally clinical outcomes as birthweight and gestation at delivery (e.g., [40]), whereas others employ a number of sociopsychological outcomes such as "love scores"[54] or postpartum attachment behavior.[55]

It is worth noting at this point that the trial by Runnerstrom[56] is not only the largest (and therefore the most influential in the overviews), but is also the trial most likely to suffer from selection biases. These biases could occur both at allocation (using casenote numbers) and after entry (by excluding complicated deliveries). Therefore, where relevant, the typical odds ratio is calculated twice, with and without the contribution of Runnerstrom's study.

Pregnancy outcomes

Gestational age at delivery (completed weeks)

Seven of the twenty-nine trials of explicit social support in pregnancy as a co-intervention give information about the preterm (< 37 com-

pleted weeks) delivery rate. They find no evidence to suggest that such support has any effect on this outcome (see figure 18.1). The same conclusion follows from the typical odds ratio based on four of the six trials in which support is the primary intervention (see figure 18.2).

Very few trials provide information about the rate of extremely preterm (< 33 completed weeks) delivery. Neither the one trial in which social support is an explicit co-intervention (see figure 18.3) or the three in which it is the primary intervention (see figure 18.4) provide conclusive evidence of an effect of social support on this rate.

Birthweight

Fifteen of the thirty-five trials in which social support in pregnancy is an explicit intervention provide some information about the low birthweight (< 2500 g) rate. The typical odds ratio based on 10 trials in which social support is an explicit co-intervention suggest that such support may result in a statistically significant reduction in this rate (see figure 18.5). The 95 percent confidence intervals of all but the last trial,[7] however, include unity. Excluding this trial from the overview shows no statistically significant effect of social support on the low birthweight rate. The same conclusion can be drawn from the five trials in which support is the primary intervention (see figure 6).

Six trials give information about the very low birthweight (< 1500 g) rate. All three in which support is a co-intervention, separately and together, suggest that such support is associated with a nonstatistically significant increase in the rate of very low birthweight (see figure 18.7). In contrast, all three trials in which support is the primary intervention suggest a nonstatistically significant decrease in the rate (see figure 18.8). Although this may be indicative of a dose effect, the numbers are small, and the confidence intervals overlap.

Discussion

It is perhaps disappointing that this overview has provided no conclusive evidence about the effects of social support in pregnancy on the two selected clinical outcomes considered above. Certainly, there are no clear implications for current practice.

There are a number of possible explanations for this continued uncertainty about the effect of such support.

It is possible, of course, that social support in pregnancy has such negligible effects that no amount of further research will provide a clear answer to whether it is either beneficial or harmful. From these overviews, particularly those in which support is the primary intervention, it is possible that there are some benefits, but that these are likely to be modest. This implies that larger numbers are needed to avoid making a "type 2" error—that is, of not being able to detect an effect, even if one exists.

Larger numbers could be obtained from two main sources. Firstly, none of the outcomes overviewed contain data from all of the 35 trials listed in table 18.1. It is possible that renewed attempts to elicit such information from their authors may yield some dividends. Not only were many of these trials carried out quite some

time ago, however, but, given their heterogeneity (particularly in the larger group of trials (29) in which support was a co-intervention), it is unlikely that such data were ever collected.

A second route to obtaining larger numbers is by increasing (from 35) the number of studies in the overview. There may be completed and published trials which we have not been able to identify from our search of the Oxford Database of Perinatal Trials. This is perhaps more likely in the field of social support than for other interventions considered in this book, as such research may not have been conducted by the clinicians nor published in the clinical journals which have been the prime sources of entry onto the data base. It is also possible that trials in which support was not the primary intervention were not coded sufficiently to ensure their identification as having support as a co-intervention. While we continue to be alert to both these possibilities, it is unlikely that concentrating on them will yield great dividends.

We are aware, however, of a number of trials from which results will be available in the near future (see table 18.2). At least four of these trials have already completed recruitment but cannot yet provide data suitable for inclusion in the overviews (see table 18.2A?). At least five more trials are still in progress (see table 18.2B?). We are also aware of other trials which are at the planning stage. As the results from these trials accumulate, we are likely to obtain more definitive answers to our questions about the effects of social support in pregnancy on the specific outcomes considered in this chapter.

A further explanation for the inconclusiveness of the results here presented is that we are considering either the "wrong" outcomes, or that these outcomes are of relevance but there are additional outcomes to which we should devote our attention.

If only because of the way in which we have chosen to present our overviews, we have implicitly assumed that low birthweight and preterm delivery are unwelcome outcomes. This assumption is certainly arguable. Both of these outcomes are to some extent proxy measures associated with adverse outcomes for the child. But there are certainly also arguments against considering low birthweight and preterm delivery as adverse in themselves, unless they are associated with a worse outcome in the longer term. Nonetheless, in general, the selected outcomes are associated with adverse events, and so may provide useful information about the effects of support.

Other outcomes are also of relevance. As indicated earlier in this chapter, we intend to review the effects of supportive interventions on other clinical outcomes, such as fetal and infant mortality and morbidity. Inevitably, some indicators of morbidity will also be proxy measures (such as Apgar scores, neonatal resuscitation, and admission to special care nurseries). We also wish to draw on the example of the work of Olds et al.[8] on child abuse, and by Gutelius et al.[9] on childhood behavior to consider possible longer term effects on the mother, the child, and the interaction between them. These examples also indicate that we plan to examine outcomes other than those which might be defined as strictly *clinical*. These can be categorized broadly as health-related behavior (such as cigarette smoking, breastfeeding, and clinic attendance) and sociopsychological outcomes (e.g., postnatal depression, satisfac-

tion with the intervention, involvement by other family members or friends in caring for the baby, and doing housework).

These are of interest both in their own right (as outcomes of the supportive intervention) and also as indications of the possible mechanisms for the effect of the support. For instance, does support, by reducing stress and depression, have some biochemical effect on fetal growth? Alternatively (or additionally), does support help to encourage pregnant women to attend regularly at antenatal clinics, thereby facilitating more effective clinical surveillance?

In addition to trying to increase the quantity and range of information in subsequent overviews of social support, we also plan to consider the quantity and type of interventions being provided. To some extent, we have begun this process of examining a dose effect by separating those interventions in which support is an explicit co-intervention (low dose) from those in which the support is the primary intervention (high dose). But we also wish to take into account the length of time over which this support is provided. The total or partial absence of social support is often a long-term problem. Hence, it may be unrealistic to seek to substantially remedy its adverse effects with a short-term dose of support in pregnancy. Indeed, it may be argued that offering and then quickly withdrawing such help may even worsen the situation. There may, therefore, be a case for increasing the dose by continuing support into early parenthood. The work conducted by Olds et al.[16] suggests that such a dose effect may, indeed, exist.

It is clear from the above discussion that the process of overview in this field (as in many others) is ongoing and (auto)dynamic. The effects of social support in pregnancy are as yet unclear, but the wealth of information which will become available over the next few years should provide some of the answers (as well as raise more questions).

At this stage, we can only concur with the conclusion by Bryce and his colleagues, that "even if the trials fail to demonstrate a benefit, the cooperation between social scientists and obstetricians to undertake this research should benefit pregnant women in that it promulgates a more holistic view of pregnancy."[2]

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Statistical Findings: Prevention of Preterm Deliveries by Home Visiting System

Table 18.1: Characteristics of Trials of Explicit Social Support in Pregnancy

Study (papers & dates)	Types of Interventions	Entry Criteria	Allocation to Interventions	Numbers	Outcomes	Inclusion Criteria (for overview)
Blondel et al. (unpublished) [1]	*Organization of care* Usual care + 1–2 home visits a week by midwives. Usual care for women with threatened preterm labor.	Women attending hospital outpatient clinics or hospitalised with threatened preterm labor; 26–36 weeks' gestation.	Random (sealed envelopes)	79 73	Costs; women's views, including satisfaction with care; birthweight; gestational age.	Social support.
Carpenter et al. 1968 [4]	*Emotional support* Interviews at intervals throughout pregnancy, labor, and the puerperium with 1st year medical students. Usual care.	Women registered in a hospital prenatal clinic.	Time of prenatal visits.	52 50	Nervousness and use of medication before, during, and after labor; length of labor.	"Provision of emotional support" (p.109).
Carter-Jessop 1981 [5]	*Preparation for parenthood* Enhancement of maternal attachment process. Usual antenatal care.	Women between 32 and 37 weeks pregnant, from private obstetricians' practices. Primiparae, white, married, expecting noncomplicated pregnancies, attendance at childbirth classes.	Random.	5 5	Postpartum attachment behavior.	"Maternal attachment process . . . enhanced by specific prenatal intervention" (p.109). "Mothers encouraged to increase awareness of fetal activity and notice how they can affect their activity" (p.111).
Cogan and Winer 1982 [7]	*Preparation for childbirth* Communication workshop to give instruction and practice in listening and responding to people's behavioral needs. Usual training.	Childbirth educators.	Random.	22 21	Parents' feelings and perceptions of events in pregnancy, labor and puerperium.	"Nonjudgmental support for expectant parents" (p.241).
Dance 1987 (unpublished) [8]	*Social support* Usual care + "link-workers" (minimum 3 home visits and 2 telephone calls). Usual care.	Immigrant Pakistani women from rural villages in Azad Kashmir and Rawlpindi, with history of 1 or more low birthweight babies, not associated with elective cesarean, gross malformation, or multiple birth.	Alternate.	25 25	Birthweight, maternal physical psychosocial health, intrapartum care, neonatal health, knowledge of health.	Antenatal support by linkworkers.

Table 18.1: Characteristics of Trials of Explicit Social Support in Pregnancy (Continued)

Study (papers & dates)	Types of Interventions	Entry Criteria	Allocation to Interventions	Numbers	Outcomes	Inclusion Criteria (for overview)
Donovan 1977 [10] Donovan et al. 1975 [11]	*Antismoking advice* Doctor at each antenatal visit giving intensive individual antismoking advice. Usual antenatal care.	Women attending antenatal clinics at 3 hospitals; smoking > 5 cigarettes daily; < 35 years; < 30 weeks' gestation; no previous perinatal deaths.	Table of random numbers.	280 308	Birthweight; gestational age; other neonatal measures; smoking in pregnancy; smoking advice; instrumental/operative delivery rate.	"Support . . . needed and contact . . . maintained" (Donovan et al. 1975, p.266).
Durham and Collins 1986 [12]	*Preparation for childbirth* Childbirth education following textbook by Hasid and tape-recorded music during conditioning exercises and relaxation/breathing techniques. Childbirth education following textbook by Hasid.	Primagravida couples receiving private childbirth education instruction.	Table of random numbers.	15 15	Frequency of intrapartum medication.	"Relaxation decreases anxiety . . . music therapy as an aid to psychological and physical control of pain" (p.268). "Music . . . provided common ground for couples to relate with each other" (p.270).
Elbourne et al. 1987 [15] Elbourne 1987 [13]	*Information feedback/sharing* Women held sole obstetric record from registration until 10 days postpartum. Women held usual cooperation cards.	Women < 34 weeks' gestation registered for antenatal care with 1 obstetrician in a peripheral antenatal clinic.	Random (consecutively numbered, sealed opaque envelopes).	147 143	Women's feelings of satisfaction, being informed, anxious, confident, in control; father's involvement; depression; health-related behavior; analgesia/anesthesia; mode of delivery; length of labor; birthweight; gestational age; administrative effects.	Hypothesized that [women holding their own obstetric notes] would feel "less anxious, more confident, more in control . . . and would find it easier to communicate with staff" (Elbourne et al., p.613).
Ellis and Hewat 1984 [16]	*Preparation for parenthood* Nurses educated about breastfeeding. Mothers given in-hospital assistance by nurse clinician and prenatal breastfeeding classes, and encouragement to telephone for support, and postnatal help. Nurses educated about breastfeeding. Mothers given in-hospital assistance by nurse clinician.	Pregnant women planning to breastfeed; able to communicate in English; cohabiting; resident in urban toll-free zone.	Random.	62 60	Breastfeeding at 1 and three months; use of semi-solids at 3 and six months.	"Encouraged to telephone nurse clinician for support" (p.1481).
Field et al. 1985 [17]	*Information feedback/sharing* Women viewed ultrasound monitor and given running descriptions. Women told about fetus well-being and gestation.	Women referred for ultrasound assessments of gestation.	Random.	20 20	Anxiety; fetal activity; maternal sleep; obstetric and postnatal complications; neonatal behavior.	"Attempt . . . to alleviate pregnancy anxiety" (p.525).

Table 18.1: Characteristics of Trials of Explicit Social Support in Pregnancy (Continued)

Study (papers & dates)	Types of Interventions	Entry Criteria	Allocation to Interventions	Numbers	Outcomes	Inclusion Criteria (for overview)
Fischer et al 1972 [18]	*Preparation for childbirth* Course on psychoprophylactic method of prepared childbirth. Two sessions with 6 couples at a time. Usual care.	Primiparae.	By EDD.	 31 41	Length of labor; analgesia in labor.	"Emphasized that martyrdom was not the point" (p.38). "Stress husband participation" (p.40).
Flint and Poulengeris 1987 [19]	*Organisation of care* 'Know your midwife' care. Team of 4 midwives throughout pregnancy, labor, and puerperium. Normal hospital care.	Women of low obstetric risk enrolling for full consultant antenatal and delivery care.	Random (sealed envelopes).	 503 498	Clinical details including birthweight; gestational age; length of labor; use of analgesia and anesthesia; mode of delivery; mothers' views.	"Mothers will experience greater emotional satisfaction."
Gutelius et al 1977 [20]	*Preparation for parenthood* Project nurse from 7th month of pregnancy. Routine health care and counseling on preparation for infant (and continuity of care for 3 years). Usual prenatal care. One visit neonatally.	Unmarried primigravidae, ages 15-18 before 7 months' gestation.	System of random numbers.	 47 48	Infant and maternal behavior.	"Counseling and anticipatory guidance" (p.294). "Frequent contact" (p.296).
Heins et al 1986 [22] Heins et al (unpublished) [23]	*Social support* Intensive antenatal care from nurse/midwife in 5 regional low birthweight clinics; social support and stress reduction; increased number of visits; assessment of cervix; education re signs of preterm labor and on health-related behavior; emphasis on weight gain; continuity of care. Usual antenatal care in high-risk clinic.	< 30 weeks' gestation; previous low birthweight baby; > 10 cm Creasy risk-scoring system; free of medical or obstetric complications (e.g., hypertension, renal disease, diabetes, or multiple pregnancy).	Random (computer-generated random numbers in sealed opaque envelopes at coordinating center, opened in response to telephone call from 1 of 5 tertiary centers).	 684 687	Birthweight; gestation at delivery; maternal weight gain.	"Social support and stress reduction."
Kehrer and Wolin 1979 [27]	*Income support* Negative income tax (i.e. families received twice monthly payments when previous month's earnings below "break even" level). No negative income tax.	Residents of low-income neighborhoods. Black head of household; at least 1 dependent < 18 years.	Random (using Watts-Conlisk allocation model).	 1028 256 771 148	Birthweight. Families Single live births.	"Income maintenance program to encourage increased utilization of prenatal care" (p.440). "May have broad influence on social behavior" (p.457).

Table 18.1: Characteristics of Trials of Explicit Social Support in Pregnancy (Continued)

Study (papers & dates)	Types of Interventions	Entry Criteria	Allocation to Interventions	Numbers	Outcomes	Inclusion Criteria (for overview)
Lilley and Forster 1986 [29]	*Anti-smoking advice* Including advice and booklets at first antenatal visit plus reinforcing letter after 2 weeks and home visit further 2 weeks later. Usual antenatal care.	Smokers (> 1 cigarette per day) at first antenatal visit; < 28 weeks' gestation.	Simple random in blocks of 8.	77 74	Smoking in pregnancy.	"Individual counseling" (p.301). "Reinforcing advice additional encouragement ... home visit" (p.310).
Little et al. 1984 [30]	*Information feedback/ sharing* A. Relaxation training. B. Relaxation training and biofeedback. C. Usual practice.	Women with BP > 135/ 85 mm Hg at 2 successive antenatal visits.	Sequentially.	18 18 24	Antenatal hospital admission; length of antenatal stay; blood pressure in late pregnancy; pregnancy outcomes.	"Extend relaxation achieved in biofeedback and relaxation sessions to stresses experienced in everyday life" (p.865).
Lovell et al. 1986 [32] Lovell et al. 1987 [33] Elbourne 1987 [31]	*Information feedback/ sharing* Women held sole obstetric record from registration to delivery. Women held usual co-operation cards.	Women attending hospital antenatal clinic at 1 obstetrician.	Random (consecutively numbered sealed envelopes).	115 120	Women's feelings of satisfaction; sense of control; communications with staff; father's involvement; health-related behavior; clinical outcomes such as birthweight, gestation, intrapartum anesthesia, length of labor, mode of delivery; administrative effects.	"Communication ... women's choices" (p.1). "Encourage information sharing and increased participation in decision making."
Oakley et al. (unpublished) [37]	*Social support* Social support including home visits by midwives, and telephone calls to women and 24-hour "hotline" to midwives. Usual antenatal care.	Previous low birthweight baby (without major malformation, multiple pregnancy, or elective delivery). Fluent English-speakers.	Random by central telephone allocation.	251 253	Birthweight; gestational age at delivery; maternal maternal and infant morbidity; maternal psychological condition postpartum; and satisfaction with care.	Social support to "influence mother's physical and mental health (antenatally and postnatally), affect process of labor and delivery ... and increase women's self-confidence about mothering."
Olds et al. 1986a [38] Olds et al. 1986b [39] Olds et al. (in press) [40]	*Social support* A. Control (no services provided through research project). B. Free transportation and regular prenatal and well-child care. C. As (B) plus nurse-home visitor during pregnancy. D. As (C) plus nurse home-visitor until child reaches 2 years of age.	Primiparous women either < 19 years or single parent or low socio-economic status; < 25 weeks' gestation.	Stratified by marital status, race, geographical regions. Assigned at random. Women drew assignment from deck of cards. Decks reconstituted periodically to over-represent treatment with smaller number of subjects (as Efron's biased coin design).	90 94 100 116	Obstetrical labor and neonatal details; use of health services; health habits including diet and smoking; gestational age at delivery; birthweight.	"Appreciation for the full set of stressful family and community influences on women's health habits and behaviors" (p.16). "Home visitation by nurses should be an effective means of ... responding flexibly to the stressful life circumstances with which socially disadvantaged women must contend" (p.17). "Parent education, enhancement of the women's informal support systems ... to emphasize the strengths of the women and their families" (p.17).

Table 18.1: Characteristics of Trials of Explicit Social Support in Pregnancy (Continued)

Study (papers & dates)	Types of Interventions	Entry Criteria	Allocation to Interventions	Numbers	Outcomes	Inclusion Criteria (for overview)
Reading et al. 1984 [43] Reading et al. 1982 [41] Reading and Cox 1982 [42] Campbell et al. 1982 [3]	*Information feedback/ sharing* High feedback—shown screen and given feedback about size, shape, and movement. Low feedback—not shown screen, global evaluation of progress.	Primiparae having real-time ultrasound at 10–14 weeks. Caucasian, in stable relationship; ages 18–32; without history of miscarriage, infertility, or risk of congenital malformations.	Random	67 62	Attitudes to scan, about pregnancy, about fetus, (especially anxiety) health related.	"Scanning . . . informative and emotionally rewarding when specific and detailed feedback made available to mother" (p.59). "Enhances awareness of fetus" (p.60). "Short-term effects on anxiety levels" (p.239).
Reading and Platt 1985 [44]	*Information feedback/ sharing* High feedback ultrasound—saw screen and nurse indicated features visualized. Low feedback ultrasound—not shown screen, global evaluation. Fetal monitoring—non-stress or contractions stress test using external fetal heart monitor. Video control—shown ultrasound record that they were aware was not their own.	High-risk population.	Random	11 8 11 7	Attitudes to scan, about pregnancy, about fetus (especially anxiety).	"Psychologic impact of technology . . . concern stressful effects" (p.907). "Anxiety levels" (p.910).
Reid et al. 1983 [45]	*Organization of care* Community antenatal clinic. Routine hospital service.	Women referred by GP from Easterhouse area for delivery at Glasgow Royal Maternity Hospital.	Random with stratification.	100 100	Obstetric morbidity and mortality; birthweight; intrapartum anesthesia and analgesia; instrumental/operative delivery rate; pattern of usage of clinics; financial effects; communication; women's perceptions of pregnancy and childbirth and reported management of first 3 months of infant life.	To deal with "failure of communication and lack of continuity of care" (p.3).
Runnerstrom 1969 [46]	*Organization of care* Obstetric care given by (1) nurse midwives (2) obstetric residents.	Women coded "uncomplicated" attending large training hospital.	Casenote numbers.	758 1005	Prenatal visits; analgesia and anesthesia; length of labor; birthweight; mode of delivery; complications; condition of baby.	"Feel full-time nurse-midwifery service with commitment to patient and family can provide more integrated and consecutive care, combatting fragmentation" (p.41).
Sammons 1984 [47]	*Preparation for childbirth* Exposure to taped music during active rehearsal of breathing patterns. Usual antenatal classes.	Women attending Lamaze childbirth classes.	Random designation of a consecutive class series.	24 30	Use of music during labor; perceived effect of music.	"Uplifting effects of music arise from music's ability to promote interpersonal relationships, to facilitate achievement of self-esteem, and to energize and bring order through rhythm" (p.266).

Table 18.1: Characteristics of Trials of Explicit Social Support in Pregnancy (Continued)

Study (papers & dates)	Types of Interventions	Entry Criteria	Allocation to Interventions	Numbers	Outcomes	Inclusion Criteria (for overview)
Sexton and Hebel 1984 [21] Hebel et al. 1985 [49]	*Anti-smoking advice* Staff assistance with smoking cessation. At least 1 personal visit supplemented by frequent telephone and mail contacts. Encouragement through information, support, practical guidance, behavioral strategies. Usual antenatal care.	Smokers of at least 10 cigarettes per day at beginning of pregnancy; < 18 weeks' gestation.	Random	463 472	Smoking habits; pregnancy outcomes; birthweight; gestational age; intrapartum anesthesia and analgesia; mode of delivery; length of labor.	"Assistance with smoking cessation . . . support" (p.919).
Shereshefsky and Lockman 1973 [50]	*Preparation for pregnancy/childbirth/parenthood* Social work counseling service. Control.	"Normal" women and their husbands during first pregnancy.	Random	? ?	Emotional disturbance in pregnancy; physical complications in pregnancy and childbirth; relationship between husband and wife in the pregnancy.	"Counseling service" (p.151). "Directed to emotional needs of pregnant women and their families" (p.152).
Spence Cagle 1984 [51]	*Preparation for pregnancy* In-class homework aimed at couple interpersonal needs for control, affection, and inclusion during pregnancy. Usual Lamaze classes.	Couples participating in Lamaze classes.	Random	? ?	Caring relationships inventory; fundamental interpersonal relations orientation behavior.	"Aimed at couple interpersonal needs for control, affection, and inclusion" (p.56).
Spencer and Morris 1986 [52] Spencer et al. (in press) [53]	*Social support* Offer of family worker. Client-centered approach. Usual care.	Women at increased risk of having low birthweight baby registering at 2 maternity units in South Manchester.	Random	655 633	Birthweight; outcome of pregnancy; gestational age; intrapartum analgesia and anesthesia; length of labor; mode of delivery.	"Social support service."
Spira et al. 1981 [54] Usual care.	*Organization of care* Domiciliary care by midwives.	Pregnant women at high risk of poor outcomes ("pathological pregnancies").	Random Operative/instrumental delivery rate.	458 425	Preterm deliveries; birthweight; death; antenatal admission.	"Continuity of care at home, not by strangers in hospital."
Sweeney et al. 1985 [56]	*Nutritional advice* Individual nutritional advice based on Higgins formula from Montreal Diet Dispensary—prescription and counseling. Usual care.	Able to communicate in English; free of pre-existing medical disorders; not private patients or teenagers; singletons.	Random (Efron's biased coin design) within pre-gravid weight, and weight gain in first 20 weeks, strata.	22 21	Maternal protein and calorie intake and maternal weight gain in late pregnancy. Antenatal, intrapartum, and postpartum maternal complications; infant birthweight and gestation at delivery.	"Providing individual care according to the specific needs of each unique mother-infant unit" (p.150).

Table 18.1: Characteristics of Trials of Explicit Social Support in Pregnancy (Continued)

Study (papers & dates)	Types of Interventions	Entry Criteria	Allocation to Interventions	Numbers	Outcomes	Inclusion Criteria (for overview)
Wiles 1984 [57]	*Preparation for breast-feeding and parenthood* Breastfeeding education class.	Primigravidae; ≥ 32 weeks' gestation; planning to breastfeed; attending childbirth education classes; vaginal delivery; no medical complications; gestation at delivery 36–43 weeks; 5 minute Apgar > 7; normally formed.	Randomly assigned (according to the class in which they were enrolled).	20	Breastfeeding; maternal perception of infant.	"Anticipatory guidance . . . for assisting parents" (p.253).
	Normal childbirth preparation class.			20		
Yanover et al. 1976 [58]	*Organization of care* Family-centered care mainly postpartum but including continuity of care from prenatal classes.	Parity 0, 1; 19–35 years old; low risk medically; 12th grade education; parents living together; father prepared to attend antenatal classes.	Random.	44	Length of labor; analgesia; anesthesia; mode of delivery; length of hospital stay; complications in mother or baby.	"Endeavor to respond to wishes of numerous families to enhance family participation . . . collaborative perinatal . . . continuity of care."
	Traditional care.			44		
Yauger et al. 1972 [59]	*Organization of care* Family-centered care; nursing service; identifying problems and needs of family and providing appropriate care. Minimum of 4 home visits.	Residents of specified areas; 3–8 months pregnant; at least 1 child < 5 years.	Random.	30	Health knowledge; health behavior; health status.	"Family-centered care . . . identification of problem and needs of family and provision of appropriate service for every member" (p.320).
	Usual care.			31		
Zimmermann-Tansella et al. 1979 [61] Dolcetta et al. 1979 [9]	*Preparation for childbirth* Prenatal classes including autogenous training—deep relaxation.	Married primiparae ages 20–35; no physical abnormalities.	Random.	14	Anxiety; pain; condition of baby, including birthweight; analgesia; length of labor; mode of delivery.	"autogenous training . . . effects of deep relaxation diametrically opposed to . . . anxiety . . . related to feelings of calmness" (p.277).
	Prenatal classes including specific gymnastic exercises.			20		

Table 18.2: Uncompleted Trials of Explicit Social Support in Pregnancy

A. Recruitment Complete Awaiting Data Analysis and Report(s)

Principal investigator and place	Nature of the intervention	Sample	Allocation	Outcomes of intervention
S. Elliott T. Leverton London, England	Social support-education groups led by psychologist or health visitor	First- and second-time mothers (N = 200)	Week of clinic enrollment	Incidence of psychiatric disorder, especially postnatal depression; psychological well-being; use of support networks; birthweight
J. King J.R. Eiser Bristol, England [28]	Supportive antismoking advice reinforced by counseling and biochemical testing at home	Smokers attending first antenatal visit (N = 300)	Random	Number of cigarettes smoked; mother's cooperation
C. Larson Montreal, Canada	Prenatal home visits by community health nurses	(N = 1,548)	Random	Health and social status of mother and child to 3 years postpartum; childrearing attitudes and behavior of mother
K. Scott Nova Scotia, Canada [48]	Enhanced maternal care from physical and lifestyle assessment by community health nurses	Women with history of low birthweight delivery (N = 10,574)	Stratified random	Patient compliance and behavior change; antenatal referrals; obstetric interventions; birthweight; stillbirths; NICU admissions; infant mortality; morbidity

B. In Progress

Principal investigator and place	Nature of the intervention	Sample	Allocation	Outcomes of intervention
S. Ng New York, U.S.A.	Intense prenatal care including weekly visit, pelvic examination, education on self-palpation; home uterine contraction monitor; social service referral	History of preterm delivery, stillbirth, or spontaneous abortion > 20/52; age < 16, > 35; registered for prenatal care before 26/52 (N = 450)	Stratified randomization so that equal numbers assigned to each treatment at any point in time	Preterm delivery; stillbirths; spontaneous abortions in 2nd or 3rd trimester; birthweight
F. Stanley R. Bryce Perth, Australia [57]	Social support via home visiting by midwives	Any of the following: previous preterm birth; perinatal death; spontaneous mid-trimester abortion; > 3 first trimester abortions; APH; low birthweight (N = 2000)	Computer-generated random numbers in blocks of 4	Preterm delivery; birthweight; cost; anxiety; social support; locus of control; conduct of labor
J. Villar E. Kestler Latin America (Argentina, Brazil, Cuba, Guatemala, Mexico)	Home visits by trained women (including nurses, social workers, and lay workers) to provide personal and family support, health education, and use of social and health services	Women attending specified antenatal clinic before 20/52, without important clinical problems, but having 1 or more risk factors: previous low birthweight birth; age ≤ 17; malnutrition; low income; maternal education, lack of support (N = 2000)	Random, stratified by center	IUGR, LBWT, preterm delivery; maternal weight gain; obstetric interventions, labor complications; breastfeeding, neonatal morbidity; use of health and social services; satisfaction; support; postpartum depression
C. Hobel R. Bemis Los Angeles, U.S.A. [25,26]	Psychosocial support/social work to reduce stress	High-risk women in 5 experimental clinics	Random assignment of clinics to experimental or control status; then random assignment of high-risk women within 5 experimental clinics to 1 of 5 interventions—1 of which is support	Gestational age at delivery; birthweight

Figure 18.1: Effect of Social Support in Pregnancy (as An Explicit Co-Intervention) on Preterm Delivery Rate (< 37 Weeks)

Study	Experiment		Control		Log Odds Ratio	Graph of Log Odds Ratios
	N	(%)	N	(%)	(95% Confidence Interval)	& Confidence Interval
						.01 .1 .5 1 2 10
Blondel, B. (unpublished)	14/79	(17.72)	11/73	(15.07)	1.21 (0.51–2.85)	
Sexton, M. J. et al. (1984)	34/429	(7.93)	40/438	(9.13)	0.86 (0.53–1.38)	
Elbourne, D. R. et al. (1987)	10/140	(7.14)	9/127	(7.09)	1.01 (0.40–2.56)	
Flint, C. et al. (1987)	31/488	(6.35)	31/479	(6.47)	0.98 (0.59–1.64)	
Lovell, A. et al. (1986)	5/95	(5.26)	4/102	(3.92)	1.36 (0.36–5.16)	
Spira, N. et al. (1981)	45/458	(9.83)	30/425	(7.06)	1.43 (0.89–2.29)	
Donovan, J. W. (1977)	14/252	(5.56)	18/279	(6.45)	0.85 (0.42–1.75)	
Typical Odds Ratio (95% Confidence Interval)					1.06 (0.83–1.34)	

Figure 18.2: Effect of Social Support in Pregnancy (as a Primary Intervention) on Preterm Delivery Rate (< 37 Weeks)

Study	Experiment		Control		Log Odds Ratio	Graph of Log Odds Ratios
	N	(%)	N	(%)	(95% Confidence Interval)	& Confidence Interval
						.01 .1 .5 1 2 10
Oakley, A. (unpublished)	14/243	(11.99)	11/243	(11.58)	1.04 (0.62–1.73)	
Spencer, B. et al. (1986)	60/602	(9.97)	54/581	(9.29)	1.08 (0.73–1.59)	
Olds, D. L. et al. (1986)	11/166	(6.63)	12/143	(8.45)	0.77 (0.33–1.80)	
Dance, J. (unpublished)	5/25	(20.00)	4/25	(16.00)	1.30 (0.31–5.44)	
Typical Odds Ratio (95% Confidence Interval)					1.03 (0.78–1.37)	

Figure 18.3: Effect of Social Support in Pregnancy (as an Explicit Co-Intervention) on Extremely Preterm Delivery Rate (< 33 Weeks)

Study	Experiment		Control		Log Odds Ratio	Graph of Log Odds Ratios
	N	(%)	N	(%)	(95% Confidence Interval)	& Confidence Interval
						.01 .1 .5 1 2 10
Elbourne, D. R. et al. (1987)	3/140	(2.14)	3/127	(2.36)	0.91 (0.18–4.56)	
Typical Odds Ratio (95% Confidence interval)					0.91 (0.18–4.56)	

Figure 18.4: Effect of Social Support in Pregnancy (as a Primary Intervention) on Extremely Preterm Delivery Rate (< 33 Weeks)

Study	Experiment n	Experiment (%)	Control n	Control (%)	Log Odds Ratio (95% Confidence Interval)	Graph of Log Odds Ratios & Confidence Interval
						.01 .1 .5 1 2 10
Oakley, A. (unpublished)	13/241	(5.35)	13/243	(5.35)	1.00 (0.45–2.20)	
Spencer, B. et al. (1986)	9/603	(1.49)	11/581	(1.89)	0.79 (0.32–1.90)	
Dance, J. (unpublished)	2/25	(8.00)	1/25	(4.00)	2.00 (0.20–20.20)	
Typical Odds Ratio (95% Confidence interval)					0.91 (0.18–4.56)	

Figure 18.5: Effect of Social Support in Pregnancy (as an Explicit Co-Intervention) on Low Birthweight Rate (< 2500 g)

Study	Experiment n	Experiment (%)	Control n	Control (%)	Log Odds Ratio (95% Confidence Interval)	Graph of Log Odds Ratios & Confidence Interval
						.01 .1 .5 1 2 10
Blondel, B. (unpublished)	9/79	(11.39)	6/73	(8.22)	1.43 (0.49–4.13)	
Sexton, M. J. et al. (1984)	29/429	(6.76)	39/435	(8.97)	0.74 (0.45–1.21)	
Elbourne, D. R. et al. (1987)	11/143	(7.69)	12/130	(9.23)	0.82 (0.35–1.92)	
Flint, C. et al. (1987)	31/478	(6.49)	38/471	(8.07)	0.79 (0.48–1.29)	
Lovell, A. et al. (1986)	5/95	(5.26)	11/102	(10.78)	0.48 (0.17–1.33)	
Reid, M. E. et al. (1983)	6/76	(7.89)	10/79	(12.66)	0.60 (0.21–1.68)	
Spira, N. et al. (1981)	51/458	(11.14)	40/425	(9.41)	1.20 (0.78–1.86)	
Donovan, J. W. (1977)	27/263	(10.27)	26/289	(9.00)	1.16 (0.66–2.04)	
Zimmerman-Tansella, C. et al. DATE?	1/14	(7.14)	1/20	(5.00)	1.46 (0.08–25.42)	
Runnerstrom, L. (1969)	61/768	(7.94)	121/1005	(12.04)	0.64 (0.47–0.87)	
Typical Odds Ratio (95% Confidence interval)					0.81 (0.68–0.97)	
Typical Odds Ratio (95% Confidence interval)			minus Runnerstrom		0.91 (0.74–1.14)	

Figure 18.6: Effect of Social Support in Pregnancy (as a Primary Intervention) on Low Birthweight Rate (< 2500 g)

Study	Experiment		Control		Log Odds Ratio	Graph of Log Odds Ratios
	N	(%)	N	(%)	(95% Confidence Interval)	& Confidence Interval
						.01 .1 .5 1 2 10
Oakley, A. (unpublished)	45/243	(18.52)	52/243	(21.40)	0.84 (0.54–1.30)	
Heins, H. C. et al. (unpublished)	118/633	(18.64)	137/642	(21.34)	0.84 (0.64–1.11)	
Spencer, B. et al. (1986)	54/602	(8.97)	50/581	(8.61)	1.05 (0.70–1.56)	
Olds, D. L. et al. (1986)	10/166	(6.02)	4/142	(2.82)	2.09 (0.71–6.11)	
Dance, J. (unpublished)	3/25	(12.00)	4/25	(16.00)	0.72 (0.15–3.51)	
Typical Odds Ratio					0.91 (0.75–1.11)	

Figure 18.7: Effect of Social Support in Pregnancy (as an Explicit Co-Intervention) on Very Low Birthweight Rate (< 1500 g)

Study	Experiment		Control		Log Odds Ratio	Graph of Log Odds Ratios
	N	(%)	N	(%)	(95% Confidence Interval)	& Confidence Interval
						.01 .1 .5 1 2 10
Reid, M. E. et al. (1983)	2/76	(2.63)	1/79	(1.27)	2.04 (0.21–19.95)	
Sexton, M. J. et al. (1987)	8/429	(1.86)	5/436	(1.15)	1.62 (0.54–4.85)	
Elbourne, D. R. et al. (1987)	3/143	(2.10)	2/130	(1.54)	1.36 (0.23–7.99)	
Typical Odds Ratio (95% Confidence Interval)					1.61 (0.68–3.81)	

Figure 18.8: Effect of Social Support in Pregnancy (as a Primary Intervention) on Very Low Birthweight Rate (< 1500 g)

Study	Experiment		Control		Log Odds Ratio	Graph of Log Odds Ratios
	N	(%)	N	(%)	(95% Confidence Interval)	& Confidence Interval
						.01 .1 .5 1 2 10
Heins, H. C. et al. (unpublished)	26/633	(3.46)	30/642	(4.67)	0.74 (0.42–1.28)	
Oakley, A. (unpublished)	4/243	(1.65)	9/243	(3.70)	0.45 (0.15–1.37)	
Spencer, B. et al. (1986)	5/603	(0.83)	6/581	(1.03)	0.80 (0.24–2.63)	
Typical Odds Ratio					0.69 (0.43–1.08)	

Inhibition of Preterm Labor: Is It Worthwhile?

MARC J.N.C. KEIRSE, M.D.

INTRODUCTION

For a normally formed infant, there is no greater risk than to be born too early in pregnancy. The transition from fetus to newborn is a hurdle to survival that is more than 100 times higher for the preterm infant than it is for the infant born at term.[1,2] Yet, there is a lack of understanding of the mechanisms that initiate labor too early in pregnancy, and there are large deficiencies in our ability to foretell and timely recognize them. Failure to understand and prevent preterm labor has made clinicians turn their attention to means and methods that could stop it in time to prevent its main consequence, preterm delivery. At first glance, they appear to have been extremely successful in doing so. Most of the approaches introduced in the past few decades have shown such high success rates in the initial reports documenting

their use that one would expect the problem of preterm labor to have been resolved many years ago (see table 19.1).

This, however, has not happened. Nor have all of these treatments disappeared from the obstetric armentarium. On the contrary, some of them have been supplemented with other treatments in the hope that two unvalidated treatments will be better than one. Thus, the term *tocolysis*, introduced by Mosler in Germany in 1964 and now generally accepted as synonymous for inhibition of labor, gave rise to the term *Zusatztokolysis* to refer to the variety of treatments that are added to either augment the effects or counteract the side effects of tocolysis. In addition, new drug treatments continue to capture the imagination of clinicians desiring to solve the issue of preterm labor once and for all. The introduction of these new treatments also continues to follow the traditional pattern in which enthusiasm for the treatment seems to be at least as compelling as evidence that it works.

What may or may not be worth inhibiting?

Preterm delivery and preterm labor

There is a widely held misconception that resolving the problem of preterm labor will resolve all of the problems associated with preterm birth. This is not so. Studies which have examined causes of perinatal mortality[1-5] have shown that more than 50 percent of that mortality is due to fetal death before the onset of labor, or to lethal congenital malformations, or both. These infants account for 12–15 percent of all preterm births, but for 60–65 percent of the mortality associated with preterm birth.[1] None of that mortality would be affected by abolishing preterm delivery, and none of these preterm labors are worth inhibiting.

What applies to mortality also applies to morbidity. This is emphasized by the fact that, currently, about one-third of preterm deliveries in singleton pregnancies do not result from spontaneous preterm labor. They result from deliberate obstetric intervention to end pregnancy because the obstetrician believes that the risks of a continuing pregnancy to mother or fetus have become unacceptably high.[1,6] The fact that approximately half of all preterm births are associated either with twin pregnancies (10%), with fetuses who died before labor or have lethal malformations (10–15%), or with elective obstetric intervention (25–30%) is rarely emphasized in the literature.[6] This may, in part, explain the failure of many preterm prevention programs to lower the (crude) incidence of preterm birth. It certainly emphasizes that, for about 40 percent of preterm deliveries, inhibition of labor is not only superfluous, but harmful.

Also readily forgotten is the fact that spontaneous preterm labor and delivery are often associated with clinically significant maternal and fetal pathology. In comparison to birth at term, preterm birth is associated with a much higher incidence of inadequate fetal growth,[7] prelabor rupture of the membranes,[8] placenta praevia,[9] placental abruption,[9] fetal congenital malformations,[2] and severe maternal disease.[9,10] Studies which have specifically addressed the incidence of maternal and fetal pathology in spontaneous preterm birth[5,10] have indicated that about half of all singleton preterm births that result from spontaneous preterm labor are asso-

ciated with such pathology. Often that pathology is the very same pathology which, in the absence of preterm labor, leads the obstetrician to artificially end pregnancy, either by induction of labor or by elective cesarean section.[1]

All of this suggests that, in many instances, nothing can be gained, but a great deal can be lost by inhibition of preterm labor and delivery.

Preterm labor and preterm contractions

Judging whether labor has started or not is by no means easy. Predicting whether it will or will not lead to delivery can be extremely difficult, as witnessed by the high "success" rates of placebo "treatments" in stopping preterm labor.[11] Lack of precision in the diagnosis of labor would create no problems if one could await the signs and symptoms that invariably clarify the diagnosis. Signs of steady progress in descent and dilatation may be useful to prepare for delivery. They are not very helpful, however, if delivery needs to be averted and if labor itself is undesirable and needs to be stopped. The more advanced labor is, the more difficult it is to stop. On the other hand, the less advanced it is, the more likely it is to stop of its own accord without any tocolytic treatment.

Successful inhibition of preterm labor, therefore, depends on early and accurate diagnosis. Early diagnosis, however, particularly diagnosis based on uterine contractions, is notoriously inaccurate for predicting whether preterm delivery will occur or not. Some[12] have even suggested that this diagnosis may be erroneous about 80 percent of the time. We recently found that 31 percent of women who came to the delivery unit with preterm uterine contractions could safely return home undelivered and without specific treatment. Several authors have attempted to improve upon the classical diagnostic criteria by measurement of hormone levels,[13,14] assessment of fetal breathing movements,[15,16] measurement of prostaglandin metabolites,[17] or assessment of thromboxane excretion.[18] Some have attempted to forestall the problem by serial cervical examinations in pregnancy,[19,20] by antenatal monitoring of uterine contractions,[21–24] or by screening for the risk of preterm delivery.[25] Some of these approaches have resulted in the administration of labor-inhibiting drugs to more than 40 percent of low-risk pregnant women,[26] demonstrating that the best results of treatment are obtained when there is nothing to be treated.

It is fair to conclude that, despite all of these attempts, the diagnosis of preterm labor has remained as problematic as ever. This has immediate consequences for the inhibition of preterm labor and for assessing the effects of tocolytic treatments. In many instances, apparently progressive preterm labor will stop irrespective of whether or not any treatment is instituted. The finding that uterine contractility is suppressed does not necessarily mean that treatment has been effective, nor does it necessarily mean that delivery will be postponed to an extent that is clinically useful.

Numerous criteria have been applied to describe "successes" of one treatment or another (see table 19.1). Some of the most commonly used treatments relate to temporary arrest of uterine contractions, number of hours or days gained before delivery, number of deliveries delayed until 36 or 37 weeks' gestation, number of infants weighing more than 2500 g at birth, and increases in mean gestational age or

mean birthweight at delivery. None of these outcomes are of great relevance to mother and baby unless they are accompanied by an increase in the number of survivors or by an increase in the quality of life for the infants and their mothers.

Early and late preterm gestations

Preterm is internationally defined as less than 37 completed weeks (259 days) of gestation,[27–29] but inhibition of labor is not equally useful at all gestational ages that are characterized as being preterm. Cut-off points drawn for demographic and public health reasons, particularly when they require international consensus, have a tendency to follow the reality of clinical practice at a safe distance rather than to light the way. This has been emphasized in the past by the expression *prematurity*, originally defined as a birthweight of 2500 g or less[30] and later defined as a gestational age of less than 37 weeks,[31] which was abolished and replaced by *preterm*[29,32] long after it had become obvious that "born too early" does not mean the same as "born too small" and that two different definitions of the same word are not very helpful in distinguishing these two situations.

The incidence of preterm delivery increases with increasing gestational age up to the cut-off point at 37 weeks. From the limited data that are available on geographically defined populations, less than one-quarter of all preterm deliveries occur below 32 weeks' gestation.[33–37]

It is particularly these deliveries, generally referred to as being *very preterm*, that present the greatest challenge. It should be realized, however, that these births also form a very heterogeneous mixture. This is exemplified in table 19.2, which summarizes some of the data on all infants with a gestational age of less than 32 weeks who were born alive in the Netherlands in 1983.[38] Even in this category (0.6% of all births in the country in 1983), which would seem to be the one most likely to benefit from inhibition of preterm labor, 15 percent of births (excluding stillbirths) resulted from deliberate obstetric intervention to end pregnancy and another 44 percent followed prelabor rupture of the membranes (see table 19.2).

Thus, the following statements appear to be true. First, the majority of preterm deliveries occur at gestational ages that are advanced enough to offer little potential for improving infant outcome by prolonging the pregnancy. Second, even at gestational ages at which the infant might theoretically benefit from prolongation of pregnancy, many other factors need to be taken into account if that theoretical benefit is to be matched by a real benefit. If delivery can be postponed or pregnancy prolonged for a duration which is thought to be clinically significant, it does not necessarily follow that the outcome for the infant will be improved. In addition, drug treatments that are powerful enough to suppress preterm labor effectively are bound to have other effects on the mother or the baby, some of them undesirable, that must be taken into account.

The conclusion of all of this should be clear. Emphasizing the uterine relaxant effects of tocolytic treatments, without considering what is gained in terms of quantity and quality of survival and without considering the possible hazards to mother and baby, is needlessly naive.

Assessment of the effects of tocolytic drugs

A large number of tocolytic agents have been employed for the inhibition of preterm labor. Not all of these are still relevant. Table 19.3 lists those that were reported to be in use in the literature of the past 10 years. Some of these, such as antibiotic treatment[59] and oxytocin analogues,[60] have been recent introductions that will require validation before being introduced into clinical practice.[61,62] Others, such as ethanol, have been used for many years,[63] but are now mainly of historical interest as witnessed by the results of questionnaire surveys conducted among obstetricians in Europe[64,65] and Australia.[66] Still others, such as magnesium sulfate[20,47,48] and diazoxide,[67] have been reported to be widely used in some centers in the United States, although there are no controlled trials which have shown them to be more effective than placebo for inhibiting preterm labor. Admittedly, magnesium sulfate has been compared with other drug treatments in four controlled trials.[50–54] Neither of these has, on balance,[41] invalidated the opinion expressed even by proponents of this tocolytic treatment that, "once labor has brought about cervical dilatation, the drug is reasonably ineffective."[47]

In the light of present day evidence, only two categories of drugs merit consideration in terms of their potential benefits for inhibiting preterm labor. These are betamimetic agents and inhibitors of prostaglandin synthesis. Calcium antagonists, although comprising a wide category of different chemical compounds with interesting properties, have been so poorly evaluated for the inhibition of preterm labor[49,54–56] that they cannot, as yet, be considered to have any clinical value for this indication.

Betamimetic drugs

Betamimetic agents are used more extensively than any of the other approaches that are employed to achieve tocolysis in preterm labor.[41,45,57] Since the first reports in 1961,[58,59] a great variety of betamimetic drugs have been applied to the inhibition of preterm labor. They have included, among others, isoxsuprine,[58,59] orciprenaline,[60] mesuprine,[61] ritodrine,[62] fenoterol,[63] salbutamol,[64] buphenine,[65] hexoprenaline,[66] and terbutaline.[67]

There is a wealth of literature on the pharmacological effects of betamimetic drugs. They are all chemically and pharmacologically related to the catecholamines, epinephrine (adrenaline) and norepinephrine (noradrenaline), and all stimulate the ß- receptors that are present in the uterus and in other organs throughout the body.[68] Many efforts have been directed at developing agents that would selectively stimulate the ß-2 receptors in the uterus. These efforts have only partially been successful, and all betamimetic agents available also stimulate to some extent ß-1 receptors. Beta-2 selectivity currently only means that interaction with ß-2 receptors occurs at lower agonist concentrations than interaction with ß-1 receptors. Stimulation of ß-1 receptors is responsible for actions such as an increase in heart rate and stroke volume, relaxation of intestinal smooth muscle, and lipolysis. Beta-2 stimulation mediates glycogenolysis and relaxation of smooth muscle in the arterioles, the bronchi, and the uterus.

Placebo controlled trials

Only three of the many betamimetic agents available (isoxsuprine, ritodrine, and terbu-

taline) have ever been compared with a control group, who received either no active treatment or placebo, for inhibition of preterm labor. Some of the drugs (such as salbutamol or fenoterol) that were reported to be used by one-third of the obstetricians in Belgium,[44] the Netherlands,[43] and the United Kingdom[45] have never been tested against placebo or no treatment in preterm labor. Yet, they entered obstetrical practice at about the same time[63,64] as other drugs, such as ritodrine[62] or terbutaline,[67-69] which have been subjected to several placebo controlled trials.

Seventeen studies have been published in which one or another betamimetic agent was reported to have been compared against no labor-inhibiting drugs in preterm labor.[5,62,67,70-85] Five of these 17 studies[72,74,75,80,81] were either conducted or reported in a manner that precludes unbiased evaluation of the treatment given. Penney and Daniell[81] reported on the use of a prolongation index for their trial, but provided no data on outcome by treatment allocation. The reasons why the four other trial reports were considered to introduce too much bias in evaluating the effects of betamimetic treatment have been elaborated by King and his colleagues.[11] Data on four unpublished ritodrine trials, conducted by Barden,[84] Hobel,[85] Mariona,[86] and Scommegna and Bieniarz,[87] and included in the report of Merkatz et al.[80] could be obtained by courtesy of the investigators and the company (Duphar) that manufactures the drug.[11] The characteristics of the resulting total of 16 (published and unpublished) trials with adequate data have been described by King et al.[11] These 16 trials involved a total of 484 betamimetic-treated women and 406 women treated with placebo or some standard treatment. All but one[75] of these trials involved the use of oral betamimetic maintenance therapy after acute tocolysis had been achieved. The large majority of the trials (12 of the 16) dealt with ritodrine, 3 tested terbutaline, and 1, the oldest trial, dealt with isoxsuprine. Allocation to the treatment or control group was stated to have been blind in 11 of the 16 trials. In the others, the method of allocation was either not described[74,78,82] or was such that the investigators may have known in advance to which group the woman would be allocated.[71,88] For 12 of the 16 trials, data were available on all women entered. That information had often not been published in the original reports, but King et al.[11] succeeded in obtaining additional data from the authors in order to minimize the introduction of bias after trial entry.[89]

King and his colleagues[11] conducted a formal meta-analysis of these 16 trials, using methods described by Peto et al.[90] and Yusuf et al.[91] This approach, which is extensively discussed by Chalmers et al.,[89] is based on calculating a ratio (odds ratio) for each trial between the odds of a particular outcome, among women allocated to betamimetic drug treatment, and the odds of the same outcome, among women allocated to the control group. The sum of the differences between active treatment and control derived from the independent trials, used in combination with the sum of the variances of these differences, is then used to calculate a typical odds ratio. The latter provides a more sensitive estimate of the effect of treatment than can be obtained from the individual, and often small trials.

This is illustrated in figure 19.1, which shows the effect of betamimetic drug treatment

on the incidence of delivery within 24 hours of trial entry in the 14 studies that provided information on this outcome. For each of the trials, the figure shows the ratio between the odds in the betamimetic treated group and in the control group, with its 95 confidence interval. An odds ratio of 1 indicates that the outcome occurs with the same frequency in the treatment as in the control group. An odds ratio of less than 1 indicates that fewer women in the treatment group delivered within 24 hours than in the control group, while an odds ratio above 1 indicates the reverse. A 95 percent confidence interval that crosses the vertical line, drawn at an odds ratio of 1, indicates that the difference between the treatment and control groups is not statistically significant. A confidence interval that does not cross the vertical line, drawn at an odds ratio of 1, indicates a statistical significance at the 5 percent level or less. The figure illustrates that there were fewer deliveries within the first 24 hours in the group allocated to betamimetic treatment than in the control group in 12 of the 14 studies, but that this reached statistical significance in only 6 of them. The typical odds ratio across trials, however, was statistically highly significant, as illustrated in figure 19.2.

Figure 19.2 shows the typical odds ratios (across trials) with their 95 percent confidence intervals for the incidences of delivery within 24 hours of trial entry, delivery within 48 hours of trial entry, delivery before 37 weeks of gestation, delivery of a low birthweight infant, respiratory distress and/or respiratory disease, and perinatal death not due to lethal congenital malformations. Further details on all of these outcomes have been described by King et al.[11]

Overall, the data from the controlled comparisons of betamimetic drug treatment in preterm labor thus convincingly demonstrate that the treatment results in a significant delay of delivery and in a lower incidence of preterm birth than observed without such treatment (see figure 19.2). As mentioned earlier, in all but one of the trials,[73] acute tocolysis was followed by oral maintenance treatment, and it is possible that this component of the betamimetic drug administration may have contributed to the overall gain in gestational age. The three placebo controlled trials that have been reported on oral maintenance treatment, after an acute episode of preterm labor had been overcome,[92,93] showed that oral maintenance treatment will to some extent prevent a recurrence of preterm labor.[41]

The data on the incidence of low birthweight also suggest a beneficial effect of betamimetic drug treatment on this outcome, although this did not reach conventional levels of statistical significance, with a 95 percent confidence interval from 0.55 to 1.02 (see figure 19.2).

The effects on delay of delivery, gestational duration, and birthweight did not, however, result in a detectable decrease in the incidence of more serious infant outcomes. The incidence of perinatal death not attributable to lethal congenital malformations and that of severe respiratory disorders, including respiratory distress syndrome, was similar in the treatment and control groups. The typical odds ratio for respiratory distress syndrome and severe respiratory disorders in the newborn across the 12 trials, which provided information on that outcome, was 1.07, with a confidence interval from 0.71 to 1.61 (see figure 19.2). Data for the individual

trials are illustrated in figure 19.3. The typical odds ratio across the 15 trials, which provided data on perinatal death, was 0.95, with a confidence interval from 0.55 to 1.67 (see figure 19.2). These results are compatible with an impressive reduction in perinatal mortality of about 40 percent, but they are equally compatible with an increase in perinatal mortality of about the same magnitude. The lack of statistical power in the individual trials is amply illustrated in figure 19.4.

The apparent lack of effect of betamimetic drug treatment on the serious adverse outcomes of mortality and respiratory morbidity may be due to a number of factors. The trials may have included too large a proportion of women in whom postponement of delivery and prolongation of pregnancy were unlikely to confer any further benefit to the baby. A treatment that is effective in stopping preterm labor at 36 weeks may well reduce the likelihood of delivery within 24 hours, of delivery before 37 weeks, and of delivering a low birthweight infant; but at that gestational age it will have little potential for reducing perinatal mortality or serious morbidity. The lack of effect on infant mortality and respiratory morbidity may also be due to adverse effects of the drug treatment. These need not be direct adverse effects, but may also result from prolongation of pregnancy when this is contrary to the best interest of the baby, as may be the case with clinically unrecognized placental abruption, severe pregnancy-induced hypertension or intrauterine growth retardation. It is also possible that too little use was made of the time gained by postponing delivery. Only four of the trial reports, for instance, indicated whether or not corticosteroids had been given before delivery, although this treatment is known to reduce perinatal mortality and morbidity.[95,96]

Controlled comparisons with other drugs

Eight reports on controlled comparisons between betamimetic agents and ethanol for the inhibition of preterm labor have appeared in the literature.[72,80,97–102] Castrén et al.[72] reported a study in which every other patient was allocated to buphenine and the others to ethanol, but this alternate allocation resulted in 43 buphenine- and 50 ethanol-treated women. This study was excluded from meta-analysis, as it was too likely to introduce bias into the comparison. The report of Merkatz et al.[81] contained no usable data on the 153 women who had been randomized to ethanol or ritodrine, but 150 of these women had been included in a previous report by Lauersen et al.,[100] and some of these had also been reported on by Fuchs.[98]

The characteristics of the trials that were less unlikely to have introduced bias into the comparison and the betamimetic agent used in these trials are summarized in table 4. Although the three largest trials all excluded some women after randomization, no attempts were made to obtain unpublished data from the authors. Widely different cut-off points have been used in these trials for describing delay of delivery, but four reports[97,99,101,102] provided information on the number of deliveries within two or three days after treatment allocation. In 2 reports this related to delivery within 48 hours;[101,102] in 1 it related to delivery within 3 days;[99] and in the other, to an insufficient delay of delivery for a full 36 hours course of corticosteroids to be given.[97] These data have been

combined in figure 19.5. The typical odds ratio of 0.38, with a confidence interval from 0.23 to 0.64, convincingly shows that betamimetic agents are superior to ethanol for delaying delivery.

Two controlled comparisons have been reported between magnesium sulphate and a betamimetic agent, either ritodrine[54] or terbutaline.[51] One of these only reported on the incidence of hypothermia with both treatments.[55] In the other report, the method of randomization was not mentioned and oral ritodrine was used for maintenance treatment in both groups.[51]

Several controlled comparisons have been conducted between different betamimetic drugs.[105-109] The interpretation of such studies is difficult, however, as the authors of the studies themselves often recognize. None of the studies has been large enough to have had a chance of detecting or excluding important differences in the outcomes that really matter, such as infant mortality and morbidity. Nor did the trials show that any one of the drugs tested was remarkably free of maternal side effects. When differences in the incidence of maternal side effects or in average gain in gestational age were detected, it is never entirely clear whether the drugs were used in equipotent doses. The wide differences among betamimetic drugs in their ratio between drug weight and drug effect make this nearly impossible to assess. Without a clearer delineation of both benefit and harm, such small differences are difficult to interpret, irrespective of whether or not they reach statistical significance. None of the studies thus far has investigated the differential in the costs of treatment between one drug and another.

Unwanted effects

A number of subjective maternal symptoms may occur as a result of betamimetic-induced changes in many bodily functions. The most frequently observed are palpitations, tremors, nausea, and vomiting. Headache, vague uneasiness, thirst, nervousness, and restlessness may also occur. Chest discomfort and shortness of breath should alert to the possibility of pulmonary congestion.

From the placebo controlled trials discussed above, there is little evidence that betamimetic drug treatment frequently poses great hazards to either mother or baby. This is not necessarily convincing in view of the fact that all 16 trials together contained less than 500 betamimetic-treated women. This is probably less than one percent of the number of women who annually receive treatment with one of these agents because they are at risk of delivering preterm. The likelihood that rare but serious adverse effects of betamimetic drugs, if they exist, would have been uncovered by any one of these trials must be infinitely small. Other data in the literature, however, indicate that these drugs are not entirely harmless.

In the late 1970s in West Germany, incidents of pulmonary edema, congestive cardiac failure, and even death started to be noticed in young women who had received the betamimetic drug, fenoterol, in combination with corticosteroids for preterm labor.[110-112] Within a year, a case of severe pulmonary edema following administration of terbutaline and dexamethasone was reported from the United States,[20] and by 1980, a large number of such reports had appeared in the medical literature.[113-123]

Initially, much of the blame for this dreadful complication was directed at corticosteroid administration, which had been the more recently introduced[96] of the two drug treatments, or at a cumulative and potentiating effect of corticosteroids and betamimetic drugs. As more of these reports became available, pulmonary edema was recognized to be a complication not only of the combination of betamimetics with corticosteroids, but also of betamimetics used alone.

Many of the cases described have been secondary to fluid overload, and no instance of pulmonary edema has been reported in women receiving betamimetics orally. Fluid overload during betamimetic treatment can occur by two mechanisms: (1) By too vigorous administration of intravenous fluids; and (2) by decreased renal excretion of sodium, potassium, and water as a direct result of high doses of betamimetics. The antidiuretic effect of betamimetics is most pronounced in the first 48 hours of tocolytic treatment, and that is when most cases of pulmonary edema are observed. In experimental animals, the development of intravascular hypervolaemia during betamimetic administration has been directly correlated with increasing doses of the betamimetics and with increasing rates of crystalloid infusion.[124] Both of these concur when betamimetic drugs are administered in dilute solutions; the higher the dose, the larger the amount of fluid.

Excessive hydration has long been practiced, apparently to combat the risk of hypotension,[125] which is rarely a problem since the betamimetic influence on blood pressure mainly consists of a widening pulse pressure, due to an increase in systolic and a decrease in diastolic pressures. Nevertheless, liberal administration of crystalloid fluids became standard practice, with as much as 400 ml[98] to 1,000 ml[74] of intravenous fluids often being administered routinely for 30 minutes even before starting infusion with betamimetics. Apparently, this practice has caused more harm than it prevented.

The frequency with which pulmonary edema develops during betamimetic drug administration is difficult to estimate. Katz et al.[126] observed clinical signs and symptoms of pulmonary edema in 5 percent of 160 women treated with terbutaline for preterm labor, but half of the women with this complication had twin pregnancies. Multiple pregnancy, as well as underlying heart disease and the use of corticosteroids or multiple drugs in addition to the betamimetic agents, is known to increase the risk of pulmonary edema. If 5 percent were a reasonable approximation of the frequency of this complication, it would have been observed and described much earlier than in the late 1970s, and it would have been noted in several of the women who participated in the placebo controlled trials. It is possible that this complication occurs more frequently with terbutaline than with other betamimetic drugs, as suggested by Robertson et al.[127] Whether or not this is true and whether or not it relates specifically to this agent or to the way in which it is administered is not clear.[69,127]

Myocardial ischaemia has been described as the other main, but rare complication of betamimetic drug treatment.[50,127–134] This complication is a separate entity from that of pulmonary edema. Diffuse micronecrosis in the myocardium has been known since 1959, when it was induced in the rat by administration of

isoproterenol.[135] Similar lesions have been observed in the myocardium after betamimetic-related death. Unlike genuine myocardial infarcts, micronecrosis is not a direct result of hypoxia. It relates to the increasing energy and oxygen requirements of the beta-stimulated myocardial cell; if demand exceeds supply, ischaemia develops.

Betamimetic drug administration results in a marked increase in cardiac output in pregnancy, which is roughly of the same order as that observed during moderate exercise.[98,136] This increase is attributed to the combination of an increase in heart rate and a decrease in peripheral vascular resistance due to relaxation of vascular smooth muscle. In late pregnancy, cardiac output is already 40 percent above prepregnancy values, and the increase is even larger in twin pregnancies.[137] The additional work imposed on the myocardium by betamimetic drug treatment may thus become too much for women with preexisting, overt, or hidden cardiac disease.[50] These women should not be given betamimetics, as the hazards for them are likely to be greater than any benefit that could be derived for their infants. For the same reason, it is wise to insist on a normal electrocardiogram before betamimetics are administered. The likelihood of finding an abnormal electrocardiogram in a normal pregnant woman without symptoms or suggestive history must be small, however. Nor can it be implied that a normal electrocardiogram before treatment will protect against subsequent development of pulmonary edema.[126,130]

A few trials have addressed the question as to whether the combination of betamimetics with other treatments could reduce some of the unwanted effects of the betamimetic drugs. Some have involved the use of different infusion fluids,[138-140] but it is clear that the amount of fluid is far more important than the type of fluid. Others have centered on the use of calcium antagonists or ß-1 receptor blockers to reduce the systemic, and especially the cardiovascular, effects of betamimetic agents. To be of value, such combination treatments should be demonstrated to achieve at least one of the following three aims. First, infant outcome in terms of mortality and serious morbidity should be better with the combined treatment than with the single treatment. Second, the addition of these drugs should decrease the incidence of serious maternal complications during betamimetic drug treatment. Third, the combined treatment should significantly decrease the incidence of less serious, but troublesome, maternal side effects. Thus far, there are no indications that any one of these goals has been adequately met.

Inhibitors of prostaglandin synthesis

There is substantial evidence that prostaglandins are of critical importance in the initiation and maintenance of human labor.[6,141] Suppression of endogenous prostaglandin synthesis is therefore a logical approach to the inhibition of preterm labor. Several agents with widely different chemical structures and pharmacokinetic properties[142] inhibit prostaglandin synthesis. They are sometimes referred to as prostaglandin synthetase inhibitors. Since there is no enzyme of this name, they are better referred to as inhibitors of prostaglandin synthesis. The inhibitors that have been used to treat preterm labor include naproxen,[143] flufe-

namic acid,[144] and acetyl salicylate,[145,146] but the most widely used has been indomethacin.[147]

All of these drugs act by inhibiting the activity of prostaglandin endoperoxide synthase, an enzyme also known as cyclooxygenase. This enzyme converts fatty acids, arachidonic acid in particular, into prostaglandin endoperoxides. It is present in high concentrations in the myometrium of pregnant women,[148] but is found throughout the body both in and outside pregnancy. Inhibition of that enzyme does not only suppress prostaglandin synthesis. It also suppresses the formation of prostacyclin and thromboxane A_2, both of which may have a number of important, though largely unknown functions in pregnancy.[141,149] Inhibition of the enzyme is not always achieved in the same way. Aspirin, for example, causes an irreversible inhibition of the enzyme, whereas indomethacin results in a competitive and reversible inhibition. This is because aspirin acetylates the enzyme, and thereby incapacitates it permanently. Indomethacin, on the other hand, competes with arachidonic acid for utilization by the enzyme; it leaves the enzyme itself intact, and, when indomethacin levels decrease, the enzyme can resume activity.

All prostaglandin synthesis inhibitors are effective inhibitors of myometrial contractility, both in and outside pregnancy. There is also no doubt that they are more effective in this respect than any of the betamimetic drugs. No case has been reported in which a betamimetic drug resulted in suppression of uterine contractility after inhibition of prostaglandin synthesis had failed, while the reverse has repeatedly been observed.[141,142,145,150,151]

Controlled comparisons

Only two studies have been reported that purported to compare a prostaglandin synthesis inhibitor with placebo in preterm labor.[152,153] Both used indomethacin as the active treatment, and both were stated to have been conducted in a double-blind manner. Neither of them was entirely placebo controlled, however, since a number of women in whom treatment was considered to have failed received other tocolytic drugs. In addition, three controlled studies have been conducted in which a prostaglandin synthesis inhibitor was either added or not added to treatment with other labor-inhibiting drugs. All of these trials also used indomethacin, while the other drug treatment used ethanol in one trial[103] and the betamimetic agent, ritodrine, in the other two.[154,155] Eight reports were available on this total of five trials.[102,152-158]

There are reservations about the heterogeneous nature of these trials and about potential bias in many of them. On the whole, these trials are of inferior quality compared with those of the placebo controlled trials of betamimetic agents. Nevertheless, the data that could reliably be extracted from all of these reports have been combined in a formal meta-analysis, the results of which are shown in figure 6. Some reservations should be expressed, however, with regard to the interpretation of these data. The results show that indomethacin, either alone or in combination, was statistically significantly more effective in delaying delivery for at least 48 hours, for at least 7 to 10 days, and beyond the preterm period than the control treatments, which consisted of placebo, ethanol, and betamimetic agents. The typical

odds ratios for these outcomes, however, are each based on only 2 of the 5 trials. There also was a statistically significant reduction in the incidence of low birthweight in the indomethacin-treated group across the 4 trials that reported on this outcome (see figure 19.6).

All reports provided data on fetal and neonatal death. Overall, the data show no reduction in the incidence of fetal and neonatal death with the use of indomethacin in preterm labor. The typical odds ratio of 0.61 had a confidence interval from 0.33 to 1.11. The incidence of respiratory distress syndrome also showed no real difference between the indomethacin and the control groups across trials, with a typical odds ratio of 0.62 and a wide confidence interval from 0.25 to 1.58.

None of the trials indicated that the use of inhibitors of prostaglandin synthesis was associated with an increased incidence of major problems for either mother or baby. On the other hand, none of these trials were truly placebo controlled, and the number of women included in these trials has not been large enough to stand a chance of uncovering rare adverse effects.

Unwanted effects

Inhibitors of prostaglandin synthesis are not innocuous. Three points need to be considered. First, there are numerous potential side effects because of the ubiquitous nature of the prostaglandins. Second, the drugs and doses that are used for inhibition of preterm labor also suppress prostacyclin and thromboxane synthesis. Third, the drugs are both chemically and pharmacologically so different from each other that they should not be considered as interchangeable.[142] They may roughly fulfill the same function, but this does not mean that they will all have the same effects and ill-effects.

The most serious potential side effects are peptic ulceration, gastrointestinal and other bleeding, thrombocytopenia, and allergic reactions. Gastrointestinal irritation is common with the use of prostaglandin synthesis inhibitors, and it can occur irrespective of the route of administration. With indomethacin it is less frequent with rectal than with oral administration, and, as the bioavailability of the drug is identical with both routes of administration,[159,160] the rectal route offers some advantage. Nausea, vomiting, dyspepsia, diarrhea, and allergic rashes have all been observed in women treated, even briefly, with prostaglandin synthesis inhibitors in preterm labor. Headache and dizziness may occur at the very start of treatment. Gamissans and his associates[157] reported systematically on the incidence of headache, maternal tachycardia above 120 beats per minute, vomiting, epigastric pain, and rectal intolerance in their trial comparing indomethacin with placebo in association with ritodrine treatment. Only two of these side effects were observed more frequently in the indomethacin-treated group. Epigastric pain was observed in 6 (4%) and rectal intolerance in 7 (5%) of 148 indomethacin treated women; these symptoms occurred in only 2 of 149 women in the control group.

Prostaglandin synthesis inhibitors cross from the mother to the fetus[161,162] and may influence several fetal functions. A great deal of information has been gathered on the fetal effects of these drugs in experimental animals. The results are not always easy to interpret,

however, because of the variety of species studied, and differences in the type of drug used and in the dose, route, and duration of administration. Apart from a prolonged bleeding time, which is a constant feature in infants born with detectable levels of such drugs, effects in human fetuses and neonates are mostly based on anecdotal reports. The most consistent observations relate to the cardiopulmonary circulation and to renal and hemostatic functions.[142]

The major worries about the use of such drugs for the inhibition of preterm labor have resulted from their influence on the ductus arteriosus. Closure of the ductus after birth consists of an initial functional closure by muscular contraction followed by definitive anatomical closure, which is a much slower process that is rarely accomplished within the first week of life. Prostaglandin synthesis inhibitors cause constriction of the ductus in the neonate, an effect that has been conclusively demonstrated in placebo controlled trials of neonatal indomethacin administration.[163,164] Autopsy and cardiac catheterization data from infants who presented with congestive heart failure at or after birth, have suggested that severe constriction of the ductus may also occur before birth in association with inhibition of prostaglandin synthesis.[119,165]

Constriction of the ductus during fetal life probably has little effect on fetal oxygenation in the short term, as effective shunting can be maintained through the foramen ovale. Prolonged prenatal constriction of the ductus arteriosus can lead to pulmonary hypertension and possibly to tricuspid insufficiency in the newborn.[119] Only two cases of persistent pulmonary hypertension have been reported in the controlled trials that we reviewed. Both of these, one in the placebo group and one in the indomethacin-treated group, occurred in Gamissans' trial in women with ruptured membranes.[154]

Wiqvist[166] compiled reports from controlled and uncontrolled clinical studies in which careful pediatric examination of the newborn had been carried out. For a total of 730 mothers included in these studies, he found 17 infants with persistent pulmonary hypertension (2.3%); 14 of these infants recovered within a few days and 3 died. A similar approach was followed by Gamissans and Balasch,[154] who found 19 cases (1.5%) among a total of 1,235 women who received prostaglandin synthesis inhibitors in preterm labor; 16 of the infants survived and 3 died. Whether or not this incidence is higher than it would have been without inhibition of prostaglandin synthesis is impossible to determine from such data.

Data both from experimental animals and human neonates suggest that the responsiveness of the ductus to indomethacin is lower at lower gestational ages. If such a difference in responsiveness exists in utero, it would imply that the risk of ductus constriction and its potential sequelae would be smallest when most gain is to be made from arresting preterm labor, and largest at gestational ages which hardly provide an indication for inhibition of labor. It is also probable, although this is not borne out by the available controlled and uncontrolled data in preterm labor, that the duration of treatment is of influence. The longer prostaglandin synthesis inhibition is continued, the greater the risk is likely to be.

Indomethacin treatment may alter both fetal and neonatal renal function. Renal dysfunction and reduced urinary output has repeatedly been noted in infants treated with indomethacin to close a patent ductus arteriosus.[167–169] The effect is apparently dose related and transient. Renal function usually returns toward pretreatment values within 24 hours after stopping the treatment.[168] Several reports have indicated impaired renal function in fetuses and in the neonates at birth following administration of prostaglandin synthesis inhibitors to the mother.[170–172] Long-term maternal treatment may influence fetal urine output enough to alter amniotic fluid volume, although other mechanisms may also be involved in the reduction of amniotic fluid volume occasionally seen during indomethacin treatment.[173] There is no evidence from either maternal or neonatal indomethacin treatment that the use of this drug in preterm labor would lead to permanent impairment of renal function in the infant.[168]

Inhibitors of the cyclooxygenase enzyme all inhibit platelet aggregation and prolong bleeding time. They do so in the mother, in the fetus, and in the neonate at birth.[28] Since neonates, and particularly preterm neonates, eliminate these drugs far less efficiently than their mothers,[142,174] these effects will be of longer duration in the baby than in the mother. There are major differences in this respect between different inhibitors of prostaglandin synthesis. Salicylates are particularly troublesome. As mentioned earlier, they acetylate the cyclooxygenase enzyme and permanently incapacitate it. Unlike most cells in the body, blood platelets cannot manufacture new enzyme. This implies that not only the cyclooxygenase enzyme, but that also the platelets themselves are rendered permanently nonfunctional. They cannot restore normal hemostasis; for this to occur, they must be replaced by new platelets.

Conclusions

Hopes that inhibition of uterine contractions can resolve the entire issue of preterm birth and its associated mortality and morbidity are unrealistic and naive, at best. On the whole, the proportion of preterm births that can be and are worth being averted by tocolytic treatment is not larger than the proportion of preterm births that is actually provoked with the same hopes of avoiding mortality and morbidity. This is not to say that there are no situations in which inhibition of preterm labor is worthwhile. Rather, it emphasizes that stopping uterine contractions does not necessarily mean improving outcome either for the mother or for the baby. Clinicians cannot escape their commitmments and they must provide care for preterm labor within the constraints of the imperfect knowledge that is available. That will include tocolytic treatment, and the main issue is how to maximize potential benefit and minimize potential harm.

In that context, only two categories of drugs presently merit consideration for the inhibition of preterm labor: Betamimetic agents and inhibitors of prostaglandin synthesis. All others are either obsolete or in an experimental stage. There is no longer a place for ethanol, relaxin, or progesterone in the treatment of preterm labor. Oxytocin analogues and calcium antagonists have been insufficiently studied to assess

whether they have any beneficial effect. The use of other drugs, such as magnesium sulphate or diazoxide, should only be permitted within the context of adequately controlled trials to determine whether or not their acclaimed benefits exist and outweigh their known adverse effects.

This does not imply that the evidence in favor of either the betamimetic agents or the inhibitors of prostaglandin synthesis is beyond reproach. On the contrary, there are many flaws in the evidence available, particularly with regard to prostaglandin synthesis inhibitors. Moreover, these two categories of drugs contain many compounds, not all of which can be assumed to have the same effects. It is also worth remembering that there are, in these wide classes of agents, drugs that have never been evaluated against "placebo treatment" in preterm labor; have never been shown to be superior to other, more validated, drug treatments; and, yet, have caused serious complications, including maternal death. Specific agents that have never been tested against placebo or no treatment, or have not been shown conclusively to be superior to others, should probably be dropped from clinical practice. There is something to be said for firmly convincing those pharmaceutical industries which propagate such agents that preterm labor is too serious a problem to be subjected to drug treatments that have not been evaluated by randomized controlled trials.

Betamimetics and prostaglandin synthesis inhibitors are effective in postponing delivery and in prolonging pregnancy. There is no evidence that the use of these drugs reduces infant mortality or morbidity. This would imply that they are only useful when the time that is gained before delivery is used to implement effective measures. Such measures could include transfer of the mother to a center with adequate facilities for intensive perinatal and neonatal care, the administration of corticosteroids to reduce perinatal mortality and morbidity, or the judicious use of "expectant management" in the period of gestation in which the infants' chances of intact survival are very poor.

Powerful drugs are dangerous when used inappropriately. Administration of these drugs in preterm labor requires a valid indication and careful control of maternal and fetal condition.

Betamimetic agents are currently the drugs of choice. For women with cardiac disease, hyperthyroidism, and diabetes mellitus, however, the risks of betamimetic drug treatment will nearly always outweigh its potential benefits. Maternal side effects are inevitable with betamimetic drug treatment, but serious complications are largely avoidable. There is no evidence that concurrent administration of calcium antagonists or ß-1 receptor blockers protects the mother against complications of betamimetic drug treatment. Nor is there any evidence that such combinations are of benefit to the baby. There is enough evidence, albeit observational, that vigorous hydration causes more harm to the mother than it prevents.

On the whole, prostaglandin synthesis inhibitors are more powerful inhibitors of uterine contractions than the betamimetic agents. There are too few data from controlled comparisons, and their quality is too poor, to recommend prostaglandin synthesis inhibitors as a first line approach in the inhibition of preterm

labor. They would appear to be the logical choice, however, if labor needs to be inhibited in women with cardiac disease, hyperthyroidism, or diabetes or if betamimetic treatment fails at very young gestational ages. Their potential hazards, weighed against potential benefits, do not justify the use of such drugs, in the doses that are necessary to inhibit uterine contractions, for any longer than is necessary (two or three days). Nor does the available evidence justify the use of aspirin and other salicylates (in the large doses that are required) for inhibition of preterm labor.

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Statistical Findings: Inhibition of Preterm Labor: Is It Worthwhile?

Table 19.1
Summary of Approaches Used to Inhibit Preterm Labor in the Past 35 Years and Their Purported Success Rates in the First English Language Publication Documenting Their Use

Agent	Year	Authors	Number of women	Criterion of success	Percent success
Relaxin	1955	Abramson and Reid [2]	5	delivery after 36 weeks	100
Isoxsuprine	1961	Bishop and Woutersz [23]	120	contractions delayed 24 hours	82
Ethanol	1967	Fuchs et al. [62]	52	delivery delayed 72 hours	67
Orciprenaline	1970	Baillie et al. [13]	30	delivery after 36 weeks	70
Mesuprine	1971	Barden [14]	17	delivery delayed 24 hours	53
Ritodrine	1971	Wesselius-DeCasparis et al. [173]	43	not delivered during treatment	80
Fenoterol	1972	Edelstein and Baillie [50]	28	delivery delayed 1 week	71
Salbutamol	1974	Liggins and Vaughan [113]	88	delivery delayed 24 hours	85
Indomethacin	1974	Zuckerman et al. [186]	50	arrest of contractions	80
Sodium salicylate	1974	Gyory et al. [72]	50	diminished uterine activity	100
Buphenine	1975	Castren et al. [33]	43	birthweight ≥ 2,500 g	86
Terbutaline	1976	Ingemarsson [80]	15	not delivered during treatment	80
Nifedipine	1977	Andersson [10]	10	delivery delayed 3 days or more	100
Magnesium sulphate	1977	Steer and Petrie [153]	31	contractions stopped 24 hours	77
Acupuncture	1977	Tsuie et al. [163]	12	delivery after 36 weeks	92
Flufenamic acid	1978	Schwartz et al. [145]	18	delivery delayed 24 hours	83
Diazoxide	1984	Adamsons and Wallach [4]	118	complete cessation of contractions	94
Oral progesterone	1986	Erny et al. [52]	57	decrease in contraction frequency	76
Oxytocin analogue	1987	Akerlund et al. [6]	13	inhibition of contractions	100

Table 19.2
Characteristics of Birth and In-Hospital Mortality and Morbidity in Infants Born Alive Before 32 Weeks (224 Days) of Gestation in the Netherlands in 1983*

Characteristics	Number	Percentage
Characteristics of birth		
After prelabor rupture of membranes	453	44.8
More than 24 h after rupture of membranes	226	22.4
After use of tocolytic drugs (any time)	533	52.8
After corticosteroid administration	173	17.1
Part of a multiple pregnancy	263	26.0
Breech presentation	293	29.0
Elective delivery†	155	15.3
Cesarean section	321	31.8

Characteristics	Number	Percentage
Characteristics and morbidity (confirmed diagnoses only) of newborn		
Congenital malformations	96	9.5
Weight below 10th centile for gestation	171	16.9
Respiratory distress syndrome	417	41.2
Intracranial hemorrhage	251	24.8
Convulsions	66	6.5
Septicaemia	133	13.2
In-hospital mortality of liveborn infants		
Neonatal deaths (28 days)	285	28.2
In-hospital deaths	310	30.7
Total	1,010	100.0

* *Data from Verloove-Vanhorick and Verwey 1987 [170].*

† *Defined as any delivery following any obstetrical intervention aimed at bringing pregnancy to an end before the onset of spontaneous labor and/or spontaneous rupture of the membranes.*

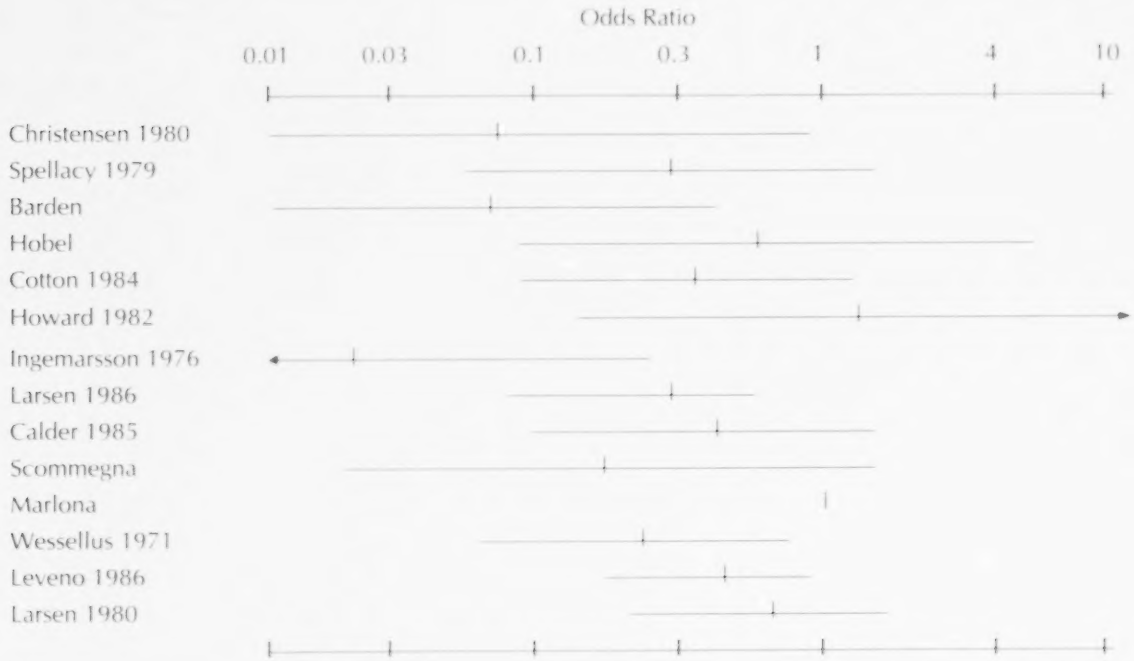
Table 19.3
Agents Reported to be Used for the Inhibition of Preterm Labor in the Literature Since 1980

Prostaglandin synthesis inhibitors	Oxytocin analogues (receptor blocking agents)	Diazoxide	Calcium antagonists
Betamimetic agents		Antimicrobial agents	Magnesium sulfate
		Ethanol	Oral progesterone

Table 19.4
Characteristics of the Trials Comparing Betamimetics With Ethanol for Inhibition of Preterm Labor

			No. randomized:reported on		
Authors (date)	Betamimetic treatment	Method of allocation	Allocated to betamimetic	Allocated to ethanol	Other details
Caritis et al. (1982)	Terbutaline iv → oral maintenance for 5 days if membranes intact	random by sealed envelopes	92:85 / \ ?:45	?:40	corticosteroids were generally given; magnesium sulphate given if assigned treatment failed; ruptured and intact membranes reported separately.
Spearing (1979)	Salbutamol iv → oral for 48 hours after contractions	alternate	22:20	22:22	salbutamol was given if ethanol failed and vice versa
Reynolds (1978)	Salbutamol iv + 200 mg sodium phenobarbitone	alternate	42:42	42:42	all ethanol treated women received 500 mg methyl prednisolone iv
Sims et al. (1978)	Salbutamol iv no maintenance	random by open list	100:88 / \ ?:42	?:46	all women randomized to betamethasone vs. placebo; 5 women ethanol → betamimetic; 2 betamimetic → ethanol
Lauersen et al. (1977)	Ritodrine iv → oral maintenance for 4 weeks or until term	random by sealed envelopes	150:135 / \ ?:68	?:67	
Fuchs (1976)					*all women are also included in the report of Lauersen et al. (1977)*

Figure 19.1
Effect of Betamimetic Drug Treatment in Preterm Labor on the Incidence of Delivery Within 24 Hours in the 14 Trials Which Provided Data on This Outcome*



* *See text for explanation on how to interpret this and subsequent figures.*

Figure 19.2
Effects of Betamimetic Drug Treatment in Preterm Labor: 'Typical' Odds Ratios, With Their 95 Percent Confidence Intervals, Across Trials for the Various Outcomes Studied

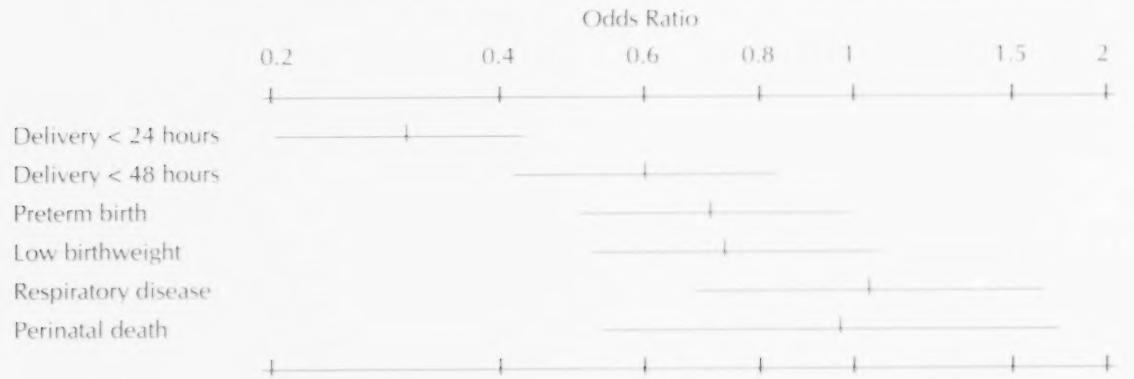


Figure 19.3
Effect of Betamimetic Drug Treatment in Preterm Labor on the Incidence of Severe Respiratory Disorders Including Respiratory Distress Syndrome

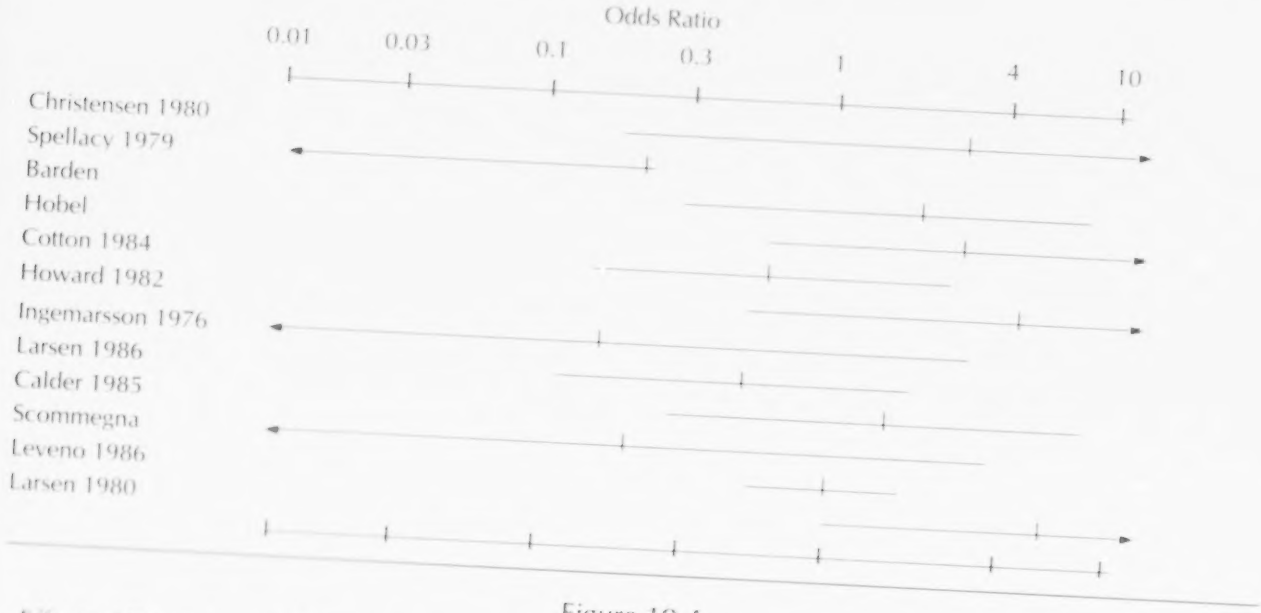


Figure 19.4
Effect of Betamimetic Drug Treatment in Preterm Labor on the Incidence of Perinatal Mortality Not Attributable to Lethal Congenital Malformations

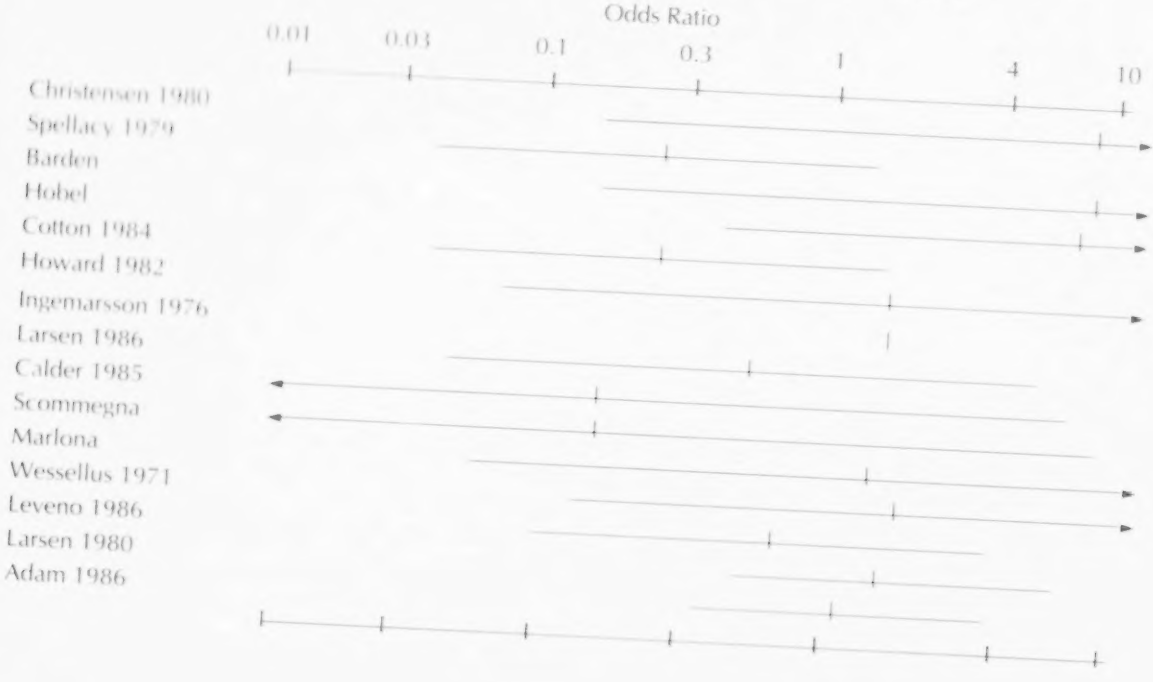


Figure 19.5
Comparison Between Betamimetic Drugs and Ethanol for Treatment of Preterm Labor: Effects on the Incidence of Delivery Within 48 to 72 Hours After Entry into the Trial

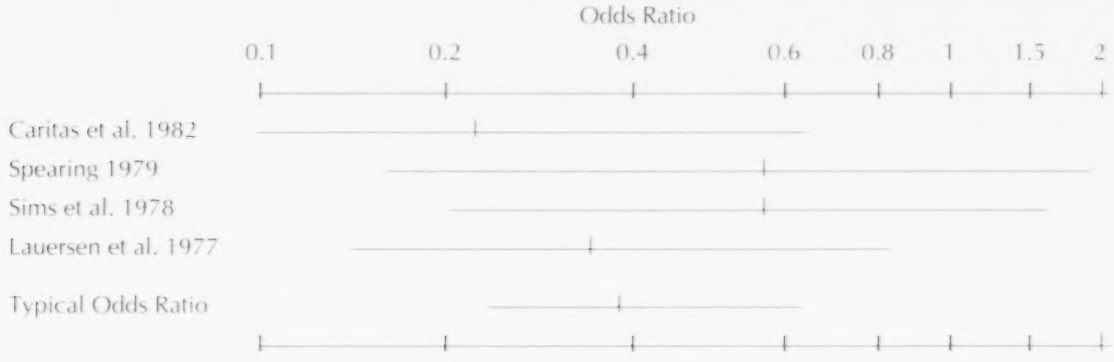
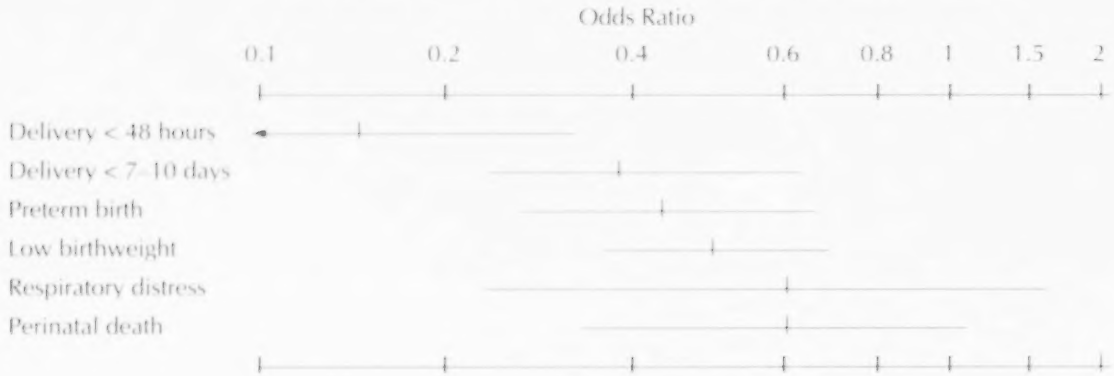


Figure 19.6
Effects of Indomethacin in Preterm Labor: 'Typical' Odds Ratios, With Their 95 Percent Confidence Intervals, Across Trials for the Various Outcomes Studied



Appendices

Appendix I: Symposium Program

Sunday, May 8, 1988

6:00 p.m.	REGISTRATION

Monday, May 9, 1988

7:30 a.m.	BREAKFAST
8:30–8:45 a.m.	SESSION I: INTRODUCTIONS *Presiders:* Heinz Berendes; Woodie Kessel; Sumner Yaffe *Rapporteur:* Phyllis Zucker *WELCOME* Duane Alexander, National Institute of Child Health and Human Development Vince Hutchins, Bureau of Matemal and Child Health and Resources Development
8:45–10:00 a.m.	SESSION II: TRENDS *Presiders:* Brian McCarthy; David Rush *Rapporteur:* Howard Hoffman
8:45 a.m.	*TRENDS IN RATES OF LOW BIRTH WEIGHTS IN THE UNITED STATES* *Speaker:* Marie McCormick, Boston, Massachusetts
9:05 a.m.	*TRENDS IN PRETERM DELIVERY AND LOW BIRTH WEIGHTS IN FRANCE* *Speaker:* Gerard Breart, Paris, France
9:25 a.m.	*DISCUSSION*
10:00 a.m.	*NUTRITION AND FITNESS BREAK*
10:30 a.m.– 1230p m.	SESSION III: DETERMINANTS *Presiders:* Ann Koontz; Charlotte Catz *Rapporteur:* Karla Damus
10:30 a.m.	*EPIDEMIOLOGICAL DETERMINANTS OF INTRAUTERINE GROWTH AND GESTATIONAL DURATION, CURRENT STATUS AND GAPS IN OUR KNOWLEDGE* *Speaker:* Michael Kramer, Montreal, Canada

10:50 a.m.	*Biological Determinants of Intrauterine Growth and Gestational Duration, Current Status and Gaps in Our Knowledge* *Speaker:* Miles Novy, Portland, Oregon
11:10 a.m.	*Behavioral Determinants of Intrauterine Growth and Gestational Duration, Current Status and Gaps in Our Knowledge* *Speaker:* Jeanne Brooks-Gunn, Princeton, New Jersey
11:30 a.m.	*Discussion*
12:30–3:30 p.m.	*Lunch*
2:00–3:30 p.m.	Session IV: Interventions *Presiders:* Henry Foster; Jose Belizan; Gian Di Renzo *Rapporteurs:* Patricia Shiono; Donald McNellis
2:00 p.m.	*The March of Dimes Preterm Birth Clinical Trial* *Speaker:* Robert Creasy, Houston, Texas
2:30 p.m.	*Results of a Three-Year Prospective Controlled Randomized Trial on Preterm Birth Prevention at the University of Pittsburgh* *Speaker:* Eberhard Mueller-Heubach, Pittsburgh, Pennsylvania
3:00 p.m.	*Discussion*
3:30 p.m.	Nutrition and Fitness Break
4:00–5:30 p.m.	Session V: Interventions *Presiders:* Marshall Klaus; Steven Ng *Rapporteur:* Margaret Freda
4:00 p.m.	*Decline and Rise of Preterm Birth Rates from a 15 Year Follow-Up Study* *Speaker:* Emile Papiernik, Paris, France
4:30 p.m.	*Update on the West Los Angeles Premature Prevention Project* *Speaker:* Cal Hobel, Los Angeles, California
5:00 p.m.	*Discussion*
5:30 p.m.	Adjourn

7:00 p.m.	DINNER *SYMPOSIUM PARTICIPANTS AND U.S. PUBLIC HEALTH SERVICE EXPERT PANEL ON THE CONTENT OF PRENATAL CARE* *Host:* Ruby Heam, Robert Wood Johnson Foundation

Tuesday, May 10, 1988

7:30 a.m.	BREAKFAST
8:30–10:00 a.m.	SESSION VI: INTERVENTIONS *Presiders:* Sara Depersio; Michael Ross; Dyanne Affanso *Rapporteur:* Jean Konte
8:30 a.m.	*THE SOUTH CAROLINA RANDOMIZED CLINICAL TRIAL USING NURSE MIDWIVES TO REDUCE LOW BIRTH WEIGHTS* *Speaker:* Henry Heins, Charleston, South Carolina
9:00 a.m.	*RESULTS FROM A REGIONAL PROGRAM BASED ON RISK ASSESSMENT TO REDUCE THE RATE OF PRETERM DELIVERY* *Speaker:* Paul Meis, Winston-Salem, North Carolina
9:30 a.m.	*DISCUSSION*
10:00 a.m.	NUTRITION AND FITNESS BREAK
10:30 a.m.– 12:30 p.m.	SESSION VII: INTERVENTIONS *Presiders:* John Kennel; David Olds; Diedre Blank *Rapporteur:* Ruth Merkatz
10:30 a.m.	*THE FAMILY WORKERS PROJECT: FINAL EVALUATION OF A RANDOMIZED CONTROLLED TRIAL OF THE PROVISION OF A SOCIAL SUPPORT SERVICE DURING PREGNANCY* *Speaker:* Brenda Spencer, Manchester, United Kingdom
11:00 a.m.	*SOCIAL SUPPORT DURING PREGNANCY* *Speaker:* Lynda Rajan, London, United Kingdom

11:30 a.m.	*Prevention of Preterm Deliveries by Home Visiting Midwives: Results of a French Randomized Controlled Trial* *Speaker:* Beatrice Blondel, Paris, France
12:00 noon	*Discussion*
12:30–2:00 p.m.	*Lunch*
2:00–3:30 p.m.	Session VIII: Interventions *Presiders:* Steven Caritis; Leslie Cooper; Lynda Rajan *Rapporteur:* Richard David
2:00 p.m.	*Smoking Interventions During Pregnancy* *Speaker:* Mary Sexton, Baltimore, Maryland
2:30 p.m.	*Results of a Multicenter Randomized Clinical Trial of Cervical Cerclage* *Speaker:* Adrian Grant, Oxford, United Kingdom
3:00 p.m.	*Discussion*
3:30 p.m.	Nutrition and Fitness Break
4:00–5:30 p.m.	Session IX: Interventions *Presiders:* Denise Main; Robert Romero; Milton Lee *Rapporteurs:* Ann Hockett; Nancy Nance
8:30 a.m.	*Use of Antiplatelet Therapy for the Prevention of Induced Preterm Deliveries by Prevention of Preeclampsia* *Speaker:* Serge Uzan, Paris, France
4:20 p.m.	*Calcium Supplementation to Reduce PIH and Preterm Delivery* *Speaker:* Jose Villar, Bethesda, Maryland
4:40 p.m.	*Magnesium Supplementation in Pregnancy, A Double-Blind Study* *Speaker:* Ludwig Spaetling, Herne, West Germany
5:00 p.m.	*Discussion*
5:30 p.m.	Adjourn

8:00 p.m. DINNER
SYMPOSIUM PARTICIPANTS AND U.S. PUBLIC HEALTH SERVICE EXPERT PANEL ON THE CONTENT OF PRENATAL CARE
Host: Richard Morton, M.D., March of Dimes Birth Defects Foundation

Wednesday, May 11, 1988

7:30 a.m. BREAKFAST

8:30–10:00 a.m. SESSION X: INTERVENTIONS
Presiders: George Rhoades; John Hauth; Tariq Siddiqi
Rapporteurs: Rose Bemis; Donald McNellis

8:30 a.m. *A RANDOMIZED CLINICAL TRIAL OF THE TREATMENT OF UREAPLASMA COLONIZATION AND PRETERM DELIVERY*
Speaker: David Eschenbach, Seattle, Washington

8:50 a.m. *DISCUSSION*

9:05 a.m. *SOCIAL SUPPORT DURING PREGNANCY: AN OVERVIEW OF CONTROLLED TRIALS*
Speaker: Diana Elbourne, Oxford, United Kingdom

9:25 a.m. *INHIBITION OF PRETERM LABOR IS IT WORTHWHILE?*
Speaker: Marc Keirse, Leiden, Netherlands

9:45 a.m. *DISCUSSION*

10:00 a.m. NUTRITION AND FITNESS BREAK

10:30 a.m.–12:30 p.m. SESSION XI: FUTURE DIRECTIONS
Presiders: Woodie Kessel; Sumner Yaffe; Heinz Berendes
Rapporteurs: Godfrey Oakley; Robert Kliegman

10:30 a.m. *DIRECTIONS FOR FURTHER RESEARCH*
Panel Moderator: Richard Behrman, Cleveland, Ohio
Panel Members: Adrian Grant, Jeanne Brooks-Gunn, Emile Papiernik, Mort Rosen, Michael Kramer, Miles Novy, Irwin Merkatz, Peter Nathanielsz

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